A Strategy for Assessing and Managing Occupational Exposures

Second Edition

John E. Mulhausen, Ph.D., CIH
Joseph Damiano, MS, CIH

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American Industrial Hygiene Association
Exposure Assessment Strategies Committee

John R. Mulhausen, Ph.D., CIH, and
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THE PRACTICE OF EXPOSURE ASSESSMENT: A STATE-OF-THE-ART REVIEW

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Each of us encounters hundreds of toxic agents everyday, without exposure and subsequent absorption (uptake) however, there is no risk of injury. Thus, exposure assessment is one of the three legs of the stool (along with toxicity assessment and dose-response assessment) upon which the practice of risk assessment rests. The field of exposure assessment has evolved out of at least 3 other disciplines over the past 50 years, including health physics, industrial hygiene, and epidemiology. Exposure assessments are a necessary component to understanding the hazard posed by exposure to naturally (e.g., aflatoxins in foods, radon in air) and nonnaturally occurring toxicants (e.g., benzene in groundwater, MTBE in air, and food additives). This article presents a thorough review of the field, including a discussion of the terminology used in exposure assessment, a description of how to quantitatively estimate dose for the major sources of exposure (food, water, air, and soil), and many of the best sources of information. In addition, techniques for assessing both variability and uncertainty are presented. Lessons learned over the past twenty years are emphasized. Some example calculations are included, nearly 400 references are cited, and a glossary of terms is provided.

Health risk assessment is the process wherein toxicology data from animal studies and human epidemiology are evaluated, a mathematical formula is applied to predict the response at low doses, and then information about the degree of exposure is used to predict quantitatively the likelihood that a particular adverse response will be seen in a specific human population (National Academy of Sciences [NAS], 1983; Paustenbach, 1995). More simply, risk assessment is a process by which scientists evaluate the potential for adverse health effects from exposure to naturally occurring or synthetic agents (Society of Toxicology [SOT], 2000). Regulatory agencies have used the risk assessment process for nearly 50 years, most notably the U.S. Food and Drug Administration (U.S. FDA) (Lehmann & Fitzhugh, 1954). However, the difference between assessments performed in the 1950s and 1960s and those performed in the 1980s and 1990s is that dose-extrapolation models, quantitative exposure assessments, and quantitative descriptions of uncertainty have been added to the process (Center for Risk Analysis, 1994). Because of increased understanding of many relevant issues, the availability of desktop computers, and better quantitative methods for predicting the low-dose response (such as physiologically based

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pharmacokinetic [PBPK] models), risk assessments conducted today provide more accurate risk estimates than in the past (Paustenbach, 1995).

Since 1980, most environmental regulations and some occupational health standards have, at least in part, been based on health risk assessments (EPA, 1998; Carnegie Commission, 1993). They include standards for pesticide residues in crops, drinking water, ambient air, and food additives, as well as exposure limits for chemicals found in indoor air, consumer products, and other media. Risk managers increasingly rely on risk assessment to decide whether a broad array of risks are significant or trivial: an important task since, for example, more than 400 of the about 2000 chemicals routinely used in industry have been labeled carcinogens in various animal studies (National Research Council, 1989, 1994). In theory, the results of risk assessments in the United States should influence virtually all regulatory decisions involving so-called "toxic agents" (National Research Council, 1996; Presidential/Congressional Commission on Risk Assessment and Risk Management [CRAM], 1997a, 1997b).

The risk assessment process has four parts: hazard identification, dose-response assessment, exposure assessment, and risk characterization (National Research Council, 1989). Although progress has been made over the past 20 years in how to conduct and interpret toxicology and epidemiology studies (e.g., hazard identification), and scientists believe that they are doing a better job of dose-response extrapolation than in the past, most significant advances in the risk assessment process have occurred in the field of exposure assessment (Wallace, 1998).

In recent years, an increasing number of environmental scientists have embraced the view that "toxicology data are important, but they do not mean much without quantitative information about human exposure." For this reason, each year since about 1990, the toxicology community has shown increasing interest in understanding the exposure assessment field (Ott, 1995b; Ott & Roberts, 1998). Fortunately, a significant amount of research has been conducted to identify better values for many exposure parameters, and major improvements have been made in applying these exposure factors to various scenarios. This article is intended to familiarize toxicologists, risk assessors, and others with this evolving field.

BASIC CONCEPTS

Description of Exposure Assessment

Exposure assessment is the step in the risk assessment process that quantifies the uptake of an agent resulting from contact with various environmental media (e.g., air, water, soil, food) (Paustenbach, 1995; U.S. EPA, 1992a; ATSDR, 1995). Exposure assessments can address past, current, or future anticipated exposures, although uncertainties can become significant when attempting to anticipate what might happen or estimate what happened long ago (Stewart & Herrick, 1991; Ripple, 1992; Paustenbach et al., 1991b, 1992b; Georgopoulos & Lioy, 1994; Duan & Mage, 1997).

Exposure assessment in various forms dates back at least to the early twentieth century, and perhaps earlier, particularly in the fields of epidemiology (Eisenbud, 1978; Lynch, 1985), industrial hygiene (McCord, 1943; Paustenbach, 1990), and health physics (Upton, 1988). Epidemiology is the study of disease occurrence and the causes of disease. Exposure assessment combines elements of industrial hygiene, radiological health, and air pollution and relies upon aspects of statistics, biochemical toxicology, large-animal toxicology, atmospheric sciences, analytical chemistry, food sciences, physiology, environmental modeling, and others (U.S. EPA, 1992c).

Fundamentally, an exposure assessment describes the nature and size of the various populations exposed to a chemical agent and the magnitude and duration of their exposures (U.S. EPA, 1988, 1996c). It determines the degree of contact a person has with a chemical and estimates the magnitude of the absorbed dose (Committee on Advances in Assessing Human Exposure to Airborne Toxicants, 1991). Several factors need to be considered when estimating the absorbed dose, including exposure duration, exposure route, chemical bioavailability from the contaminated media (e.g., soil), and, sometimes, the unique characteristics of the exposed population (e.g., hairless mice absorb a greater percent of chemical than other mice). By definition, "duration" is the period of time over which the person is exposed.

Knowledge of the chemical concentration in an environmental medium is essential to determine the magnitude of the absorbed dose. This information is usually obtained by analytical measurements of samples of the contaminated medium (air, water, soil, sediment, food, or dust). Estimates can also be made using mathematical models, such as models relating air concentrations at various distances from a point of release (e.g., a smoke stack) to factors including release rate, weather conditions, distance, and stability of the agent (Zannetti, 1992; Scott et al., 1997a). Needless to say, a significant number of factors need to be considered to quantitatively evaluate a typical contaminated site (Figure 1).

In general, since about 1995, our ability to perform exposure assessments has matured to a degree that they will usually possess less uncertainty than other steps in the risk assessment. Admittedly, many factors should be considered when estimating exposure; for example, it is a complicated procedure to understand the transport and distribution of a chemical that has been released into the environment. Nonetheless, available data indicate that scientists can now do an adequate job of quantifying chemical concentrations in various media, and the resulting uptake by exposed persons, if they account for the majority of factors that should be considered (Paustenbach et al., 1997c). For those who wish to question this assertion, consider our level of confidence that animal bioassays which label a chemical a possible human carcinogen even though tumors were observed in a mouse liver only at the maximum tolerated dose (MTD). Similarly, consider our confidence in dose-extrapolation when three equally

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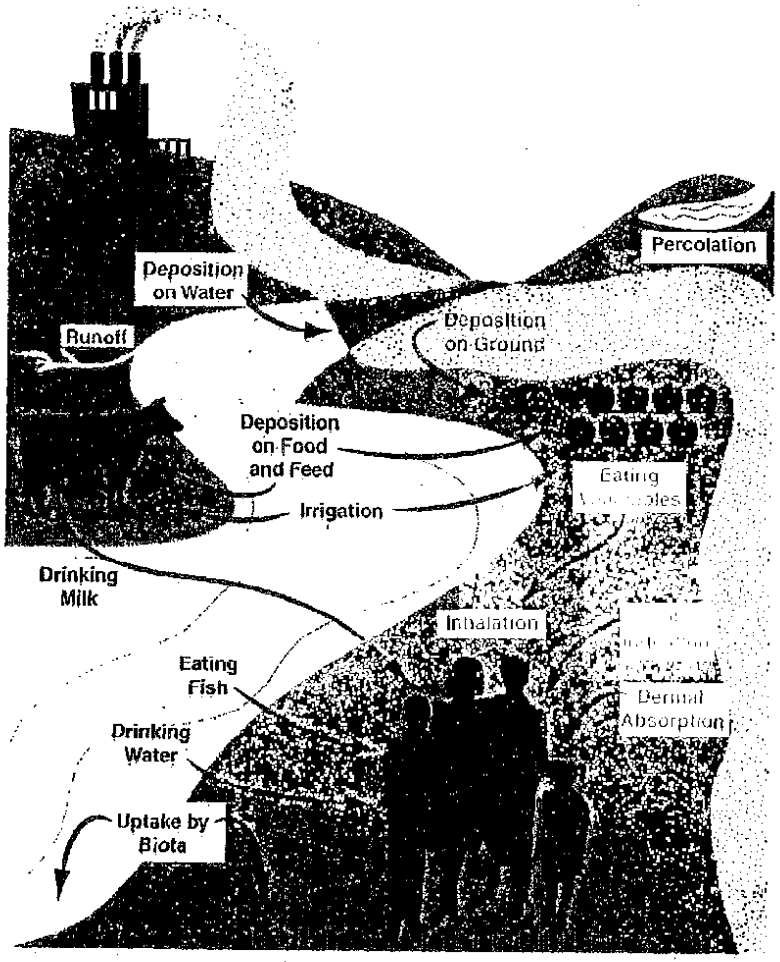

FIGURE 1. Exposure pathways.

valid models yield risk estimates that are 1000-fold different at a typical environmental dose?

The primary routes of human exposure to chemicals in the ambient environment are dust and vapor inhalation, dermal contact with contaminated soils or dusts, and ingestion of contaminated food, water, dust, or soil. In the workplace, the predominant exposure route usually is inhalation, followed

by dermal uptake and, to a lesser extent, dust ingestion due to hand-to-mouth contact (Paustenbach et al., 1999). Uncertainty in environmental exposure assessment is usally less than in an occupational exposure assessment. In many workplaces, there can be large fluctuations in airborne concentrations, a significant difference in work practices of different persons, and there is real difficulty in measuring dermal uptake and incidental ingestion (Paustenbach, 1990; Paustenbach et al., 1986; Jayjock et al., 2000).

Scientists in the field of radiological health were the first to quantitatively estimate human uptake of environmental contaminants (Romney et al., 1963); health physics publications can be a source of valuable information when conducting assessments of chemical contaminants (Baes et al., 1984). This work, which was conducted after World War II, provided numerous methodologies for estimating human uptake of environmental contaminants. These have been refined over the past decade (McKone & Bogen, 1991; Fries & Paustenbach, 1990; ILSI, 1998). The availability of information on the degree of exposure associated with various scenarios has increased dramatically over the past 15 years, as evidenced by the size of the recent *EPA Exposure Factors Handbook*, a four-volume document containing nearly 1000 pages of information on exposure assessment (U.S. EPA, 1996c, 1996d, 1996e, 1997b).

The practice of exposure assessment, at least for regulatory purposes, has changed over time. For example, beginning in the late 1970s, regulatory policy in the United States encouraged or mandated the use of conservative approaches when conducting exposure assessments. This was codified in the U.S. EPA original document entitled *Risk Assessment Guidance for Superfund*, called RAGS (U.S. EPA, 1989). At that time, standardization of exposure assessments used to satisfy regulatory agencies was considered prudent because it guaranteed that risks would not be underestimated in order to ensure protection of public health. Beginning about 1985, concern evolved that repeated use of conservative exposure factor assumptions was producing unrealistically high estimates of exposure (Paustenbach, 1989a; Paustenbach et al., 1986; Nichols & Zeckhauser, 1988; Maxim, 1989; Cullen, 1994) and that the cost of achieving the recommended clean-up levels was becoming enormous. Thus, to improve the accuracy of many of the factors used in these assessments, a significant amount of new research was initiated.

Around 1990, risk assessors learned how to apply Monte Carlo techniques to evaluate both typical and highly exposed persons. Application of Monte Carlo techniques to exposure assessment has dramatically improved our understanding of the certainty of our estimates, and has decreased the problems associated with the repeated use of conservative assumptions, thereby altering the field permanently (Thompson & Burmaster, 1991; Thompson et al., 1992; Finley & Paustenbach, 1994; Burmaster & Harris, 1993). The U.S. EPA and other agencies have now embraced this approach,

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which is well described in the recent document called RAGS3A (a process for conducting probabilistic risk assessment) (U.S. EPA, 1999b).

What Is Exposure?

Because there has been no agreed-upon definition of where or when exposure takes place, terminology used in published exposure assessment literature has been inconsistent. Although there is reasonable agreement that human exposure means contact with the chemical or the agent (U.S. EPA, 1989, 1992a; Allaby, 1983), there has not yet been widespread agreement as to whether this means contact with (1) the visible exterior of the person (e.g., an aluminum strip touches the skin but can't be absorbed), or (2) the so-called exchange boundaries where absorption takes place (skin, lungs, gastrointestinal tract) (U.S. EPA, 1992c). The differing definitions have led to some ambiguity in the use of terms and units for quantifying exposure.

Some scientists find it helpful to think of the human body as having a hypothetical outer boundary that separates the inside of the body from the outside (U.S. EPA, 1992c). The outer boundary of the body consists of the skin and openings into the body, such as the mouth, nostrils, or punctures and lesions in the skin. In most exposure assessments, chemical exposure is defined as contact of the chemical with some part of this boundary. An exposure assessment is the quantitative or qualitative evaluation of that contact. It describes the intensity, frequency, and duration of contact, the route of the chemical across the boundary (exposure route, e.g., dermal, oral, or respiratory), the resulting amount of chemical actually crossing the boundary (dose), and the amount of chemical absorbed (internal dose) (U.S. EPA, 1992a; Leung & Paustenbach, 1994). These categories can be further refined as described below; however, a very workable quantitative definition of exposure is to think of it as "the product of (concentration), (time), and (duration), or rate of transport of toxicant (mg/cm^2-min)" (Jayjock et al., 2000).

Depending on the purpose of the exposure assessment, the numerical output of these analyses may be an estimate of either exposure or dose. If an exposure assessment is being done as part of a risk assessment in support of an epidemiologic study, for example, sometimes only qualitative exposure levels are all that can be provided. In these situations, categories like low-, medium-, and high-level exposure may be used. In contrast, most assessments of environmental or occupational exposure conducted in recent years attempt to quantitatively predict the absorbed dose (mg/kg-d) and, occasionally, the circulating blood level or the concentration of the toxicant in the target organ (Paustenbach et al., 1988; Reitz et al., 1996).

Concepts of Exposure, Intake, Uptake, and Dose

The process of a chemical entering the body can be described in two steps—contact (exposure), followed by actual entry (crossing the boundary). Absorption, either upon crossing the boundary or subsequently, leads

to the availability of an amount of chemical to biologically significant sites within the body (target tissue dose). Although the description of contact with the outer boundary is simple conceptually (e.g., mg benzene/cm^2 skin), estimating the degree to which a chemical crosses this boundary is somewhat more complex.

In the early 1990s, some scientists described the transport of chemicals into the body as involving two separate steps: intake and uptake. Intake involved physically moving the chemical in question through an opening in the outer boundary (usually the mouth or nose), typically via inhalation, eating, or drinking. Normally, the chemical was contained in a medium such as air, food, water, or dust/soil. Here, the key question was the mass inhaled or ingested. Uptake, in contrast to intake, involved absorption of the chemical through the skin or across other barriers.

Today, most persons tend to lump intake and uptake together, simply calling the amount of chemical entering the body "uptake." In some cases, chemicals are absorbed completely, so systemic absorption (uptake) is the same as that eaten or in contact with the skin (intake). In other cases, the chemical is often contained in a carrier medium, and the medium itself typically is not absorbed at the same rate as the "contaminant of interest," so estimates of the amount of chemical crossing the boundary cannot be made directly. For example, benzene on the surface of a contaminated soil particle will move quickly through the skin, but benzene in the center of the soil particle may never completely reach the surface, and therefore it is not bioavailable and will not enter the bloodstream. Of course, for many inorganic chemicals like arsenic or lead in soil, oral and dermal bioavailability can be very low since the chemical is bound to the interstices of the soil particle and, therefore, uptake is very low. In short, if a chemical cannot be released from a media, it has no bioavailability and, consequently, since there is no uptake the chemical does not pose a risk.

Dermal absorption is an example of direct uptake across the outer boundary of the body. A chemical uptake rate is the amount of chemical absorbed per unit of time. In this process, mass transfer occurs by diffusion, so uptake will depend on the concentration gradient across the boundary, permeability of the barrier, and other factors (Leung & Paustenbach, 1994; McDougal et al., 1990; McKone, 1990). Chemical uptake rates can be expressed as a function of the exposure concentration, permeability coefficient, and surface area exposed, or as flux (Paustenbach et al., 1999).

Bioavailability

The study of the bioavailability of chemicals in various media began around 1980 and continues to be an important topic (Ruby et al., 1999).

Most studies are of oral bioavailability, although the dermal and inhalation bioavailability of chemicals have also been evaluated. This area of research has been a bit confusing due to a lack of standard terminology (Hrudey et al., 1996). A recent review paper by Ruby et al. (1999)

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is probably the most authoritative one on this topic. The following definitions should be used in future assessments.

Bioavailability: Oral bioavailability is defined as the fraction of an administered dose that reaches the central (blood) compartment from the gastrointestinal tract. Bioavailability defined in this manner is commonly referred to as *absolute bioavailability,* and is equal to the oral absorption fraction.

Relative bioavailability: Relative bioavailability refers to comparative bioavailabilities of different forms of a substance or for different exposure media containing the substance (e.g., bioavailability of a metal from soil relative to its bioavailability from water), expressed in this document as a relative absorption factor (RAF).

Relative absorption factor: The RAF describes the ratio of the absorbed fraction of a substance from a particular exposure medium relative to the fraction absorbed from the dosing vehicle used in the toxicity study for that substance (the term *relative bioavailability adjustment,* RBA, is also used to describe this factor).

Bioaccessibility: The oral bioaccessibility of a substance is the fraction that is soluble in the gastrointestinal environment and is available for absorption. It is imortant to note that the bioaccessible fraction is not necessarily equal to the RAF (or RBA) but depends on the relation between results from a particular in vitro test system and an appropriate in vivo model.

There are both in vitro and in vivo tests for evaluating bioavailability, and many different approaches have been suggested over the past 20 years (Umbreit et al., 1986a; Lucier et al., 1984; Shu et al., 1988; Jayjock et al., 1996; Hrudey et al., 1996).

As noted by Ruby et al. (1999), a number of in vitro tests are available. Simple extraction tests have been used for several years to assess the degree of metals dissolution in a simulated gastrointestinal-tract environment. The predecessor of these systems was developed originally to assess the bioavailability of iron from food, for studies of nutrition. In these systems, various metal salts or soils containing metals are incubated in low-pH solution for a period intended to mimic residence time in the stomach. The pH is then increased to near neutral, and incubation continues for a period intended to mimic residence time in the small intestine. Enzymes and organic acids are added to simulate gastric and small-intestinal fluids. The fraction of lead, arsenic, or other metals that dissolves during the stomach and small-intestinal incubations represents the fraction that is bioaccessible (i.e., is soluble and available for absorption).

A number of in vivo tests have also been used with varying success. For example, gastrointestinal absorption of lead in humans varies with the age, diet, and nutritional status of the subject as well as with the chemical species and the particle size of lead that is administered. For example, age is a well-established determinant of lead absorption; adults typically absorb 7–15% of lead ingested from dietary sources, while estimates of lead absorption from dietary sources in infants and children range from 40 to 53%. For the purpose of modeling exposure to lead in soil, the U.S. EPA currently assumes that the absolute bioavailability of lead in diet and water is 50% and that the absolute bioavailability of lead in soil is 30% for children. This corresponds to a soil RAF of 0.60 (60%) for the bioavailability of soil lead relative to lead in water (i.e., RAF = 0.3/0.5) (Ruby et al., 1999).

The results of bioavailability studies need to be considered in virtually all assessments involving human exposure. Often the effects in uptake will be minor, while in other cases one may find that insignificant quantities of a chemical are absorbed even though the applied dose or exposure is quite high (Umbreit et al., 1986a; Van Den Berg et al., 1984).

Applied Dose or Potential Dose

Applied dose has been defined as the amount of chemical available at the absorption barrier (skin, lung, gastrointestinal tract) (U.S. EPA, 1992c). It is useful to know the applied dose if a relationship can be established between the applied dose and the internal dose, a relationship that can sometimes be established experimentally. This relationship can be estimated either through modeling or by direct measurement. For example, some researchers have analyzed phenol concentrations in the blood of volunteers over time after placing their hands in a bucket of nitrobenzene in an attempt to quantify the flux rate (Piotrowski, 1967, 1977). Usually it is difficult to measure the applied dose directly, as many of the absorption barriers are internal to the human, and not localized in such a way to make measurement easy. An approximation of applied dose can be made, however, using the concept of potential dose (U.S. EPA, 1992c).

Potential dose is simply the amount of chemical that is ingested or inhaled, or the amount of chemical contained in material applied to the skin. It is a useful term or concept in those instances when there is a measurable amount of chemical or transport medium. The potential dose for ingestion and inhalation is analogous to the administered dose in a dose-response experiment.

For the dermal route, potential dose is the amount of chemical applied, or the amount of chemical in the medium applied (for example, as a small amount of soil deposited on the skin). Note that because all of the chemical in the soil particulate is not contacting the skin, this differs from exposure (the concentration in the particulate times the duration of contact) and applied dose (the amount in the layer actually touching the skin) (U.S. EPA, 1992c).

As previously noted, the amount of chemical that reaches the exchange boundaries of the skin, lungs, or gastrointestinal tract may often be less than

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the potential dose if the material is only partly bioavailable. For example, only about 0.001% to 1.0% of dioxins or polycyclic aromatic hydrocarbons (PAHs) on fly ash in contact with the skin are likely to penetrate (Shu et al., 1988). When bioavailability data are known, adjustments to the potential dose should be made to convert it to the absorbed or internal dose (Shu et al., 1988; Hrudey et al., 1996).

Internal Dose

The amount of chemical that has been absorbed and is available for interaction with biologically significant receptors (e.g., target organs) is called the *internal dose*. Estimating internal dose is the first objective of a good exposure assessment (Ramsey & Andersen, 1984; U.S. EPA, 1996b).

Transport models are available to assist in this process (McKone & Bogen, 1992). Once absorbed, the chemical can be metabolized, stored, excreted, or transported within the body. The amount transported to an individual organ, tissue, or fluid of interest is termed the *delivered dose* (Clewell, 1995). The delivered dose may be only a small part of the total internal dose. For example, although 1 mg of PCB may be absorbed into the body, at any given time the amount in the liver (the target organ) may only be 0.001 mg. Work to refine the techniques used to estimate delivered dose has been among the most exciting areas of exposure assessment research over the past 15 years. Currently, the best approach to estimate delivered dose is to directly measure blood or to use physiologically based pharmacokinetic (PBPK) models (Andersen et al., 1991; Lilly et al., 1998).

The *biologically effective dose* (BED), or the amount that actually reaches cells, sites, or membranes where adverse effects occur (National Research Council, 1990), may represent only a fraction of the delivered dose, but it is obviously the best one for predicting adverse effects. To understand BED is the ultimate goal of exposure assessment. Thus far, toxicologists have rarely been able to estimate BED or measure it for most chemicals (U.S. EPA, 1992c), but models allow us to estimate it.

Currently, most risk assessments dealing with environmental chemicals (as opposed to pharmaceutical assessments) rely upon dose-response relationships based on the potential (administered) dose or the internal dose, because our understanding of how to estimate the delivered dose or the biologically effective dose is insufficient for most chemicals. In general, the best method currently available for estimating the dose to the target organ is to use PBPK models. These have been developed for about 60 high-volume industrial chemicals (Leung & Paustenbach, 1995) (Table 1).

Often it is more convenient in risk assessment to refer to dose rates, or the amount of a chemical dose (applied or internal) per unit time (e.g., mg/d), or as dose rates on a per unit body weight basis (e.g., mg/kg-d). Most exposure data found in the various editions of the U.S. EPA *Exposure Factors Handbook* and other guidance documents are presented as dose

TABLE 1. PBPK Models for Toxic Substances

Benzene	Lead
Benzo[a]pyrene	Methanol
Butoxyethanol	Methoxyethanol (2-ME)
Carbon tetrachloride	Methyl ethyl ketone (MEK)
Chlorfenvinphos	Nickel
Chloralkanes	Nicotine
Chloroform	Parathion
Chloropentafluorobenzene	Physostigmine
cis-Dichlorodiammine platinum	PBB
Dichloroethane	PCBs
Dichloroethylene	Styrene
Dichloromethane	Toluene
Dieldrin	TCDF
Diisopropylfluorophosphate	TCDD (Dioxin)
Dimethyloxazolidine dione	Tetrachloroethylene
Dioxane	Trichloroethane
Ethylene oxide	Trichloroethylene
Ethyoxy ethanol (2-EE)	Trichlorotrifluoroethane
Formaldehyde	Vinyl chloride
Hexane	Vinylidene fluoride
Hexavalent chromium	Xylene
Kepone	

Note. This table is an expansion of one presented in a paper by Leung and Paustenbach (1995).

rates (e.g., grams of fish consumed each day) rather than as dose (U.S. EPA, 1996c, 1996d, 1996e; American Industrial Health Council, 1994).

Exposure and Dose Relationships

Depending on the purpose of the exposure assessment, different estimates of exposure and dose may require calculation. Often, estimates of uptake will be presented in units used in the toxicology study which may not be useful for exposure calculations.

When risk is a function of time of exposure, exposure or dose profiles can be very useful. In these profiles, the exposure concentration or dose is plotted as a function of time (Aylward et al., 1996). Concentration and time are used to depict exposure, while amount and time characterize dose.

Such profiles are important for use in risk assessment where the severity of the effect depends on the pattern by which the exposure occurs, rather than on the total (integrated) exposure. For example, a developmental toxicant may only produce effects if exposure occurs during a particular stage of development. As shown in Figure 2, during the time above a certain dose rate (the shaded portion), there was an increased risk to the fetus of certain birth defects. Similarly, a single acute exposure to very high dose may induce adverse effects, even if the average is much lower than apparent no-effect levels. To understand the probability of an adverse effect, one

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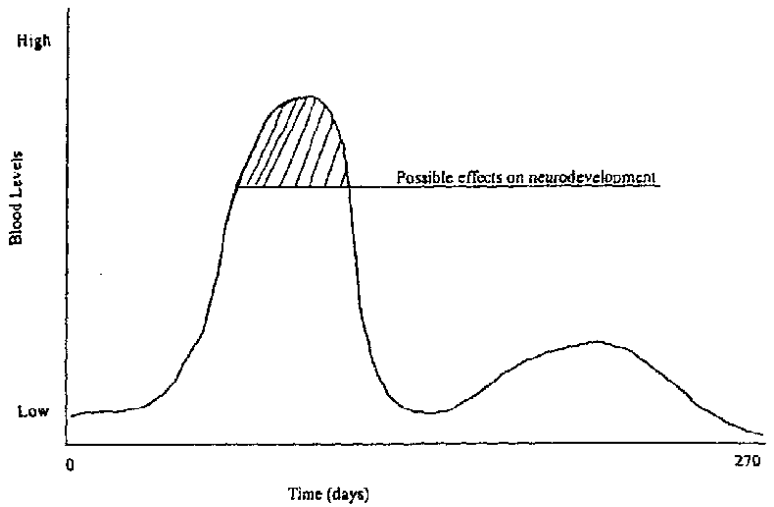

FIGURE 2. Time course of exposure to a developmental toxicant.

must generally consider the pharmacokinetics of the specific chemical. For example, for a chemical that has a long biologic half-life, internal exposure continues long after the chemical is ingested because blood levels remain high until the substance is completely released from poorly perfused tissues like adipose, and then is metabolized and/or eliminated.

In general, there is a need to consider the time elements of exposure assessment. Specifically, it is useful to understand the relationship between the biological half-lives of toxicants and the subsequent critical time element of their exposure. Indeed, the appropriate consideration of these elements should drive the specified averaging times for both toxicant exposure limits and exposure assessment (Roach, 1966; Paustenbach, 2000).

If a chemical or agent causes its biological damage quickly and is gone from the body in a short time, then how we test its toxicity is critical. For example, consider a material with a half-life of a few minutes in the body. If we were to test it by spreading or apportioning the daily dose of this material over 24 h via inhalation, it will produce a different toxicity than if the animal got the same amount in a couple of 1-h inhalation exposures. The same dose of this quick-acting material would do much more damage amassed in a bolus dose of a few minutes or even an hour or two than spread over 24 h.

Thus, dosing times in toxicological studies should be commensurate with the biological half-life for the relatively quick-acting chemicals. We often need to measure the exposure over an appropriately short period of time where the worst-case exposure may occur. The same logic also holds for the dermal (topically applied) and oral (normally ingested) exposures in

that they should occur in time frames that are comparable to what we would expect in use. Bolus dosing by gavage or injection would, of course, be worst case.

On the other hand, if the biological half-life of the compound is longer than a few days, then relatively high spikes of exposure over a day or two are not particularly significant from a health impact perspective. What is important from a chronic toxicity perspective for these types of compounds is, of course, the weighted average over a significantly longer time period.

As such, it would only seem appropriate to use an annual average exposure when you are dealing with a compound with a very long (greater than 90 d) half-life in the body and no evidence of acute toxicity at high short-term dose rates (Roach, 1966; Rappaport, 1985; Rappaport & Spear, 1988).

Aggregate exposure is the sum total of exposure to a chemical via all routes of exposure (and all media). It is now commonplace to add as many as 6 to 10 different exposure sources per route (e.g., DDT in different fruits and vegetables) and 3 exposure routes (e.g., DDT via food, air, and dermal contact). The units of aggregate exposure are concentration times duration. Aggregate exposure has been considered in complex assessments of the past 10 yr, such as for incinerators, but it came to the fore with the passage of the Food Quality Protection Act (FQPA) in 1996. At least one major symposium and the resulting publication tackle this subject. Ample guidance from regulatory agencies and examples of how to perform these assessments will undoubtedly be published over the next 5 yr (International Life Sciences Institute [ILSI], 1998).

Integrated exposure is the total "area under the curve" (AUC) of the exposure profile. An exposure profile (a picture of the exposure concentration over time) is particularly useful when trying to understand occupational exposure because it contains more information than a numerical estimate of the integrated exposure, including the duration and periodicity of exposure, the peak exposure, and the shape of the area under the time-concentration curve (Figure 2). The risk posed by most systemic toxicants with chronic effects are often best understood by evaluating the blood concentration versus time relationship.

The last way to characterize exposure is the time-weighted average (TWA). This is particularly relevant when conducting a carcinogen risk assessment. In cancer risk assessments, the time over which exposure is integrated is usually 70 yr (U.S. EPA, 1992c). A TWA dose rate is the total dose divided by the time period of dosing, usually expressed in units of mass per unit time, or mass/time normalized to body weight (e.g., mg/kg-d). TWA dose rates such as the lifetime average daily dose (LADD) are used in dose-response equations to estimate lifetime risk.

Measures of Dose

For risk assessment purposes, dose estimates should be expressed in a manner that can be compared with available dose-response data from ani-

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mal or human studies. For example, if data on human exposure are in milligrams of lead per deciliter of blood (mg/dl), it would be best to use the blood concentrations in an animal or human study to predict the risk. Frequently, dose-response relationships are based on potential dose (called administered dose in animal studies), although dose-response relationships are sometimes based on internal dose. These differences need to be accounted for. The measure of dose selected should be based on the mode of action of the adverse effect (U.S. EPA, 1992a, 1996b; Aylward et al., 1996; Andersen et al., 1995; Andersen & Conolly, 1998). For example, to assess a nasal irritant, the airborne concentration of the chemical is a relevant dose, and an even better dose metric would be mg of chemical contacting a square centimeter of nasal mucosa.

Doses may be expressed in several different ways. Solving Eq. (1), for example, gives the dose rate over the time period of interest. The dose per unit time is the dose rate, which has units of mass per time. The most common dose measure is average daily dose (ADD), which is used to predict or assess the noncarcinogenic effects of a chemical.

$$\text{ADD} = (C \cdot \text{IR} \cdot D \cdot B)/(\text{BW} \cdot \text{AT}) \quad (1)$$

where ADD is the potential average daily dose, BW the body weight, B the bioavailability, AT the time period over which the dose is averaged (days), C the mean exposure concentration, and IR the ingestion rate.

The following presents a typical calculation.

Example Calculation 1: Determining the Average Daily Dose A typical American eats a certain amount of lettuce over a lifetime (about 2000 kg). Assume that on any given week, the maximum quantity ingested is 0.5 kg, and the maximum on any one day is 0.04 kg/d. Assume that the typical aldrin residue is 4 mg/kg on all lettuce ingested over the person's lifetime. What is the ADD of aldrin for the maximum week? Assume the oral bioavailability of aldrin in lettuce is 90%.

Given:

C = 4 mg/kg (aldrin)
D = 1 week
BW = 70 kg
AT = 7 d
IR = 0.5 kg/wk
B = 0.9

Therefore:

$$\text{ADD} = (C \cdot \text{IR} \cdot D \cdot B)/(\text{BW} \cdot \text{AT})$$
$$\text{ADD} = (4\ \text{mg/kg})(0.5\ \text{kg/wk})(0.9)/(70\ \text{kg})(7\ \text{d})$$
$$\text{ADD} = 0.004\ \text{mg/kg-d}$$

When the primary health risk posed by a chemical is cancer or another chronic effect, then the biological response is usually described in terms of lifetime probabilities (e.g., the increased risk of developing cancer during a 70-yr lifetime is 2 in 100,000). In these circumstances, even though exposure may not occur over the entire lifetime, doses are usually presented as LADDs (U.S. EPA, 1992c). The LADD takes the form of Eq. (2), with lifetime (LT) replacing the averaging time (AT):

$$\text{LADD} = (C \cdot \text{IR} \cdot D \cdot B)/(\text{BW} \cdot \text{LT}) \quad (2)$$

Example Calculation 2: Determining the Lifetime Average Daily Dose Assume that the reasonable maximum ingestion lifetime uptake of lettuce over a 70 yr lifetime (99% person) is 14,000 kg and that it contains 4 mg/kg of Aldrin. What is the LADD?

Given:

C = 4 mg/kg (aldrin in lettuce)
IR = 14,000 kg
D = 70 yr
B = 0.9
BW = 70 kg
LT = 70 yr ≈ 25,550 d

where

$$\text{LADD} = (\bar{C} \cdot \overline{\text{IR}} \cdot \bar{D} \cdot \bar{B})/(\text{BW} \cdot \text{LT})$$

Then

$$\text{LADD} = (4)(14{,}000/70)(70)(0.9)/(70)(25{,}550)$$
$$\text{LADD} = 0.028\ \text{mg/kg-d}$$

Although other measures of chronic dose may be more appropriate for predicting the hazard posed by specific chronic toxicants, such as an area under the blood concentration (AUC) curve or the peak target tissue concentration, the LADD is the most common dose metric used in carcinogen risk assessment (Figure 3).

CONCEPTUAL APPROACHES TO EXPOSURE ASSESSMENT

Quantifying Exposure

Although exposure assessments are conducted for a variety of reasons, the process of estimating exposure can be approached using one of the following three methods (U.S. EPA, 1992c):

1. Direct measurement: The exposure can be measured at the point of contact (the outer boundary of the body) while it is taking place, measuring the exposure concentration and time of contact and integrating them (point-of-contact measurement). An example is the measurement of the amount of contaminated soil on an exposed hand of someone digging a hole to plant a tree. The relevant exposure information would be contaminant concentration in soil (μg/g), surface area of the hand in contact with the soil (100 m^2), and time of exposure (2 h).

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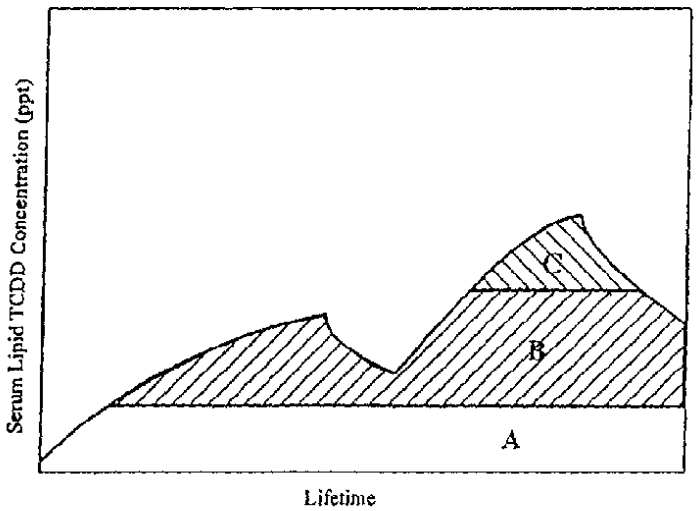

FIGURE 3. Theoretical concentration versus time curve for TCDD illustrating one possible relationship between AUC and response. This figure illustrates the possible combination of AUC and thresholds for production of various responses: area A, no effect; area B, enzyme induction occurs; area C, significant increased cell proliferation. From Aylward et al. (1996).

2. Exposure scenario: Sometimes one is concerned about an exposure that may or may not occur, so a hypothetical exposure scenario is developed. In these assessments, specific data cannot actually be collected, but relevant information can be found. For example, if an incinerator were built, it would not be known today how much of each chemical in the airborne emissions would reach the various compartments in the environment (food, soil, sediment, surface water), but one can describe what would be likely to occur (a scenario).
3. Biomonitoring: Sometimes historical exposure can be estimated based on the amount of chemical in the body or being eliminated in breath, urine, or feces. In recent years, doses have been reconstructed through internal indicators (biomarkers, body burden, excretion levels) for persistent organics and several metals. Among the best examples are lead in blood, phenol in urine, volatile hydrocarbons in the breath, and dioxins in blood fat.

These three approaches to exposure quantification (or dose) are independent because each is based on different assumptions and/or data. The fact that they are independent measures is useful in verifying or validating the results of the various approaches. Each of the three has strengths and weaknesses; using them in combination can considerably strengthen the

credibility of an exposure assessment (National Research Council, 1994; U.S. EPA, 1992a; U.S. Office of Science and Technology Policy, 1993). For example, results of the exposure assessment would be validated if one could mathematically predict the absorbed dose per day of a chemical, estimate the resulting blood concentrations, and confirm these estimates by sampling the blood of the exposed population (Paustenbach et al., 1997c).

Estimates Based on Direct Measurement

Point-of-contact or direct exposure assessment evaluates the exposure as it occurs. Measuring chemical concentrations at the interface between the person and the environment as a function of time yields an exposure profile. The best known example of point-of-contact measurement is the output of a radiation dosimeter. This small badgelike device measures radiation exposure as it occurs and provides an integrated exposure estimate for the period of time over which the measurement has been taken (U.S. EPA, 1992c). The Total Exposure Assessment Methodology (TEAM) studies (U.S. EPA, 1987b) conducted by the U.S. EPA made use of direct measurements. In the TEAM studies, a small pump with a collector and an absorbent was attached to a person's clothing to measure his or her exposure to airborne solvents or other pollutants as it occurred, just as has been done in industrial hygiene studies of the past 60 yr (ACGIH, 1998). In both of these examples, the measurements are taken at the interface between the person and the environment while exposure is occurring.

The area of exposure assessment known as agricultural hygiene has developed very sophisticated techniques for estimating the uptake (absorption) of chemicals during the mixing and application of pesticides. These have been described in numerous articles (Knaak et al., 1989, 2000). A recent paper by Kissel and Fenske (2000) is also useful.

Providing that the measurement devices are accurate, the direct measurement method likely gives the best exposure value for the period of time over which the measurement was taken. It is often expensive, however, to use these techniques to evaluate persons in the community, and measurement devices and techniques do not currently exist for all chemicals (at least at ambient concentrations).

Estimates Based on Exposure Scenarios

Using the exposure scenario approach, the assessor attempts to estimate or predict chemical concentrations in a medium or location and link this information with the time that individuals or populations are in contact with the chemical. An exposure scenario is the set of assumptions describing how this contact takes place. This is, by far, the most common approach to exposure assessment. Such an approach is necessary when trying to predict the impact of events that may occur in the future, such as building a new manufacturing facility or introducing a new pesticide or

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herbicide (Proctor et al., 1997; Paustenbach et al., 1991a; 1991b; Nessel et al., 1991).

The first step to building a scenario is to determine the concentration of the contaminated media. This is typically accomplished indirectly by measuring, modeling, or using existing data on concentrations in the media of concern, rather than at the point of contact (for example, pesticide residues on food or metal emissions on residential soils). Often, we assume that the concentration in the bulk medium is the same as the concentration at the point of exposure. This can be a source of potential error and should be discussed in the uncertainty analysis. For example, over the past 20 yr, most assessments of the hazard posed by contaminated soil were based on soil samples collected in the top 6 in of soil, even though most persons were exposed routinely to the surface soil (usually the top ½–2 in). Arguments can be made in either direction about the appropriateness of this assumption.

The next step in conducting an exposure scenario is to estimate the contact time, identify who is likely to be exposed, and then develop estimates of the exposure frequency and duration. Like chemical concentration characterization, this is usually done indirectly using demographic data, survey statistics, behavior observation, activity diaries, activity models, or, in the absence of more substantive information, assumptions about behavior (U.S. EPA, 1997b, 1997d).

Chemical concentration and population characterizations are ultimately combined in an exposure scenario. One of the major problems in evaluating dose equations is that the limiting assumptions used to derive them (e.g., steady-state assumptions) do not always hold true. Two approaches to this problem are available: (1) to evaluate the exposure or dose equation under conditions when the limiting assumptions do hold true, or (2) to build a dynamic model that accounts for both accumulation and degradation. The microenvironment method, which is usually used to evaluate air exposures, is an example of the first approach. This method evaluates segments of time and location when the assumption of constant concentration is approximately true, and then sums the time segments to determine the total exposure for the respiratory route, effectively removing some of the uncertainty (Price et al., 1996b). In occupational hygiene, this is done by combining time–motion data with short-term air concentration data. While exposure concentration and time of contact may be estimated in some situations, the concentration and time of contact can be measured for each microenvironment. This avoids much of the error due to summing average values in cases where concentration and time of contact vary widely.

In the second approach, a computer model can efficiently predict dose if enough data are available (Lynch, 1985; Zannetti, 1992; Calabrese & Kostecki, 1992). When conducting modeling, there are various tools used to describe parameter variation, such as Monte Carlo analysis, and these may be necessary in some assessments.

Estimating Exposure Using Biological Monitoring

Exposure can often be estimated after it has taken place. The key factor is whether the biological half-life of the chemical is sufficiently long to allow for accurate measurement. If a total dose is known or can be reconstructed, and information about intake and uptake rates is available, an average past exposure rate can be estimated (Aylward et al., 1996; Smith et al., 1993; Plato et al., 1995; Stewart et al., 1996; Sathiakumar et al., 1998). Dose reconstruction relies on measuring biological fluids (blood, urine), hair, nails, or feces after exposure, intake, and uptake have already occurred, and using these measurements to back-calculate dose (Aylward et al., 1996). However, data on body burden levels or biomarkers cannot be used directly unless a relationship can be established between these levels (or biomarker indications) and internal dose.

Biological monitoring can be used to evaluate the amount of a chemical in the body by measuring one or more parameters (Table 2). In general, if these measurements can be made and the biologic half-life is acceptable, then past exposure estimates can be reasonably accurate. Not all of these can be measured for every chemical (U.S. EPA, 1992c). Following is a list of possible measurements:

- The concentration of the chemical itself in biological tissues or sera (blood, urine, breath, hair, adipose tissue, etc.).
- The concentration of the chemical's metabolite(s).
- The biological effect that occurs as a result of human exposure to the chemical (e.g., alkylated hemoglobin or changes in enzyme induction).
- The amount of a chemical or its metabolites bound to target molecules.

The results of biomonitoring can be used to estimate chemical uptake during a specific interval, if background levels do not mask the marker and the relationship between uptake and the selected marker is known (DeCaprio, 1997). The sampling time for biomarkers is often critical. Establishing a correlation between exposure and measurement of the marker, including pharmacokinetics, is necessary to properly back-calculate historical exposure (U.S. EPA, 1992c).

The strengths of this method are that it demonstrates that exposure and absorption of the chemical has actually taken place, and theoretically it can give a good indication of past exposure. The drawbacks are that (1) it will not work for every chemical because of interferences or the reactive nature of the chemical, or because the biological half-life of the agent is too short; (2) that the approach has been applied to only a few chemicals; (3) that data relating internal dose to exposure are needed; and (4) that it may be expensive.

For those chemicals where biological monitoring can be used to estimate past exposure, the information obtained can be invaluable for conducting retrospective exposure assessments that can be used in epidemi-

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TABLE 2. Examples of Types of Measurements to Characterize Exposure-Related Media and Parameters

Type of measurement (sample)	Usually attempts to characterize (whole)	Examples	Typical information needed to characterize exposure
Breath	Total internal dose for individuals or population (usually indicative of relatively recent exposures).	Measurement of volatile organic compounds (VOCs), alcohol. (Usually limited to volatile compounds.)	1. Relationship between individuals and population; exposure history (i.e., steady-state or not) pharmacokinetics (chemical half-life), possible storage reservoirs within the body. 2. Relationship between breath content and body burden.
Blood	Total internal dose for individuals or population (may be indicative of either relatively recent exposures to fat-soluble organics or long-term body burden for metals).	Lead studies, pesticides, heavy metals (usually best for soluble compounds, although blood lipid analysis may reveal lipophilic compounds).	1. Same as for breath. 2. Relationship between blood content and body burden.
Adipose	Total internal dose for individuals or population (usually indicative of long-term averages for fat-soluble organics).	NHATS, dioxin studies, PCBs (usually limited to lipophilic compounds).	1. Same as for breath. 2. Relationship between adipose content and body burden.
Nails, hair	Total internal dose for individuals or population (usually indicative of past exposure in weeks to months range; can sometimes be used to evaluate exposure patterns).	Heavy metal studies (usually limited to metals).	1. Same as for breath. 2. Relationship between nails, hair content and body burden.
Urine	Total internal dose for individuals or population (usually indicative of elimination rates); time from exposure to appearance in urine may vary, depending on chemical.	Studies of tetrachloroethylene and trichloroethylene.	1. Same as for breath. 2. Relationship between urine content and body burden.

Source. U.S. EPA (1997a).

ology studies. Some examples of chemicals for which past exposure can reliably be estimated include several metals, as well as numerous large organic chemicals (e.g., DDT, chlordane, dioxin, polybrominated biphenyl (PBB), PCB) (Aylward et al., 1996).

INFORMATION UPON WHICH EXPOSURE ASSESSMENTS ARE BASED

Comprehensive exposure assessment of a complex scenario may require several hundred exposure factors to estimate the various chemical concentrations in one of several dozen different media. Among the most complex exposure assessments are those that address the risks posed by airborne emissions from combustors (Fries & Paustenbach, 1990; U.S. EPA, 1997d; Price et al., 1996) (Figure 4). To estimate the concentration, numerous dispersion models, as well as fate and transport models, may be required. In addition, the assessor may need to search the literature to identify relevant studies from as many as 10 related fields of research. Sometimes, hundreds of published papers and government guidance documents need to be evaluated, used, and cited. In short, the exercise can be formidable, especially for assessments involving food chain contamination. Equally difficult and highly complex exposure assessments are those that attempt to estimate the uptake of fish by various members of the angling public (Wilson et al., 2000).

Obtaining Data on Intake and Uptake

The numerous editions of the *Exposure Factors Handbook* (U.S. EPA, 1996c, 1996d, 1996e, 1997b) present statistical data on many of the factors used to assess exposure, including intake rates, and these provide citations for primary references. Today, this series of publications represents the most comprehensive, single source of exposure assessment information. Some of the many intake factors in the various volumes include:

- Drinking water consumption rates.
- Breast milk ingestion rates for infants.
- Consumption rates for homegrown fruits, vegetables, beef, and dairy products.
- Consumption rates for recreationally caught fish and shellfish.
- Incidental soil ingestion rates.
- Pulmonary ventilation rates.
- Surface area of various parts of the human body.
- Body weight for various age groups.

Table 3 presents examples of some of the standard or default exposure factors used in risk assessment.

The *Exposure Factors Handbook* is updated routinely to include additional factors and to include new research data on previously discussed fac-

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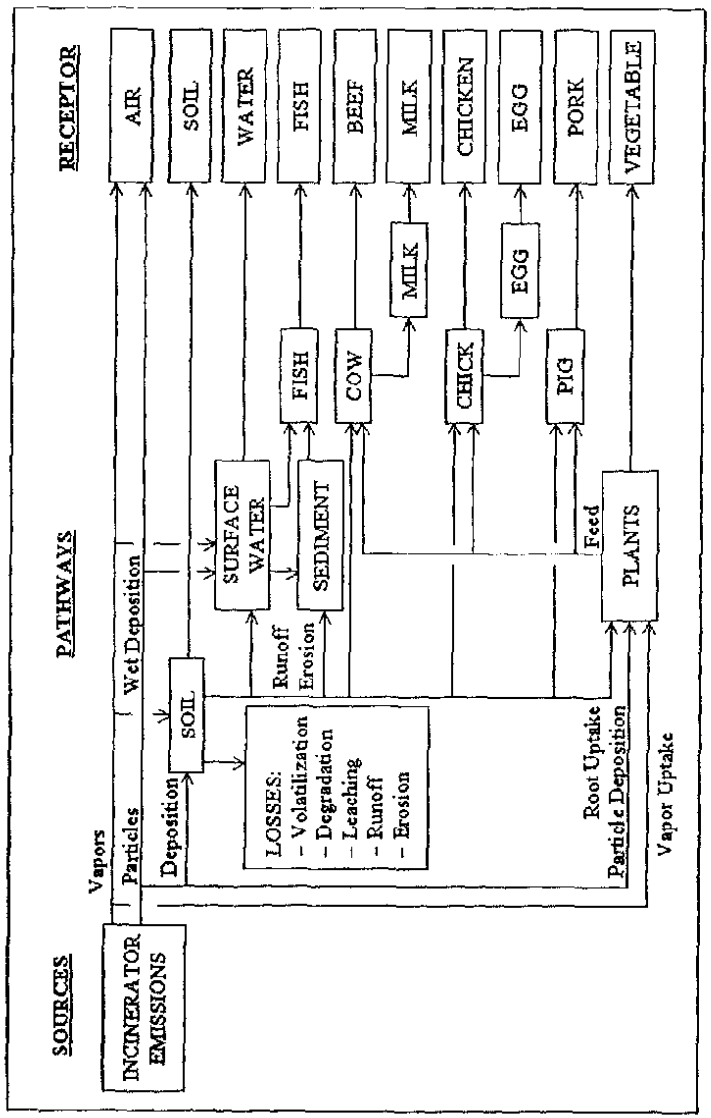

FIGURE 4. EPA's conceptual approach to dealing with direct and indirect exposure pathways as illustrated by assessments of incinerator emissions.

tors. It also provides default parameter values, which can be used when site-specific data are not available. Obviously, general default values should not be used in place of known, valid data that are more relevant to the assessment being conducted. The U.S. EPA handbook, though substantial, may not contain all available information on exposure factors or relevant studies, so a supplemental literature search should be conducted to ensure that pertinent literature has been identified. As discussed later, if a probabilistic or Monte Carlo assessment is to be conducted, the document titled *Risk Assessment Guidance for Superfund: Process for Conducting Probabilistic Risk Assessment* (U.S. EPA, 1999b) and other publications should be consulted.

TABLE 3. Some Standard Regulatory Default Assumptions Used In Exposure Assessment

Variable	Assumption
Drinking water	2 L/d (RME adult)
	1.4 L/d (adult ave.)
	1.0 L/d (child)
	0.1 L/d (incidental ingestion during swimming)
Soil (ingestion)	200 mg/d (child ave.)
	800 mg/d (child 90th percentile)
	100 mg/d (adult)
Food	2000 g/d (adult total)
Beef (home-grown)	44 g/d (ave.)
100 g/d (all sources)	75 g/d (RME)
Dairy (home-grown)	160 g/d (ave.)
400 g/d (all sources)	300 g/d (RME)
Fruit (home-grown)	28 g/d (ave.)
140 g/d (all sources)	42 g/d (RME)
Vegetables (home-grown)	50 g/d (ave.)
200 g/d (all sources)	80 g/d (RME)
Sport fish	30 g/d (ave.)
	140 g/d (RME)
Inhalation	10 m^3/d (ave. 8-h shift.)
	20 m^3/d (adult ave.)
	30 m^3/d (RME)
Body weight	13.2 kg (2–5 yr)
	20.8 kg (6 yr)
	70 kg (adult ave.)
Lifespan	70 yr
Exposed skin area	0.2 m^2 (adult ave.)
	0.53 m^2 (adult RME)
	1.94 m^2 (male bathing)
	1.69 m^2 (female bathing)
Showering	7 min (ave.)
(5-min. shower uses 40 gal)	12 min (90th percentile)
Residence time	9 yr (ave.)
	30 yr (RME)

Note. RME, reasonable maximum exposure; ave., average.

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Concentration Measurements in Environmental Media

Sometimes the existing chemical concentration data are inadequate to conduct a proper site-specific assessment. In these cases, concentration data can be gathered by conducting a new field study, or by evaluating data from past field studies and using them to estimate concentrations. Media measurements taken close to the point of contact are preferable to measurements far removed geographically or temporally. As the distance from the point of contact increases, the certainty of the data at the point of contact usually decreases, and the obligation for the assessor to show relevance of the data to the assessment at hand becomes greater. For example, an outdoor air measurement, no matter how close it is taken to the point of contact, cannot by itself adequately characterize indoor exposure (Paustenbach et al., 1997b).

Concentrations often vary considerably from place to place, seasonally and over time due to changing emission and use patterns (Scott et al., 1997a, 1997b; Paustenbach et al., 1986). This needs to be considered not only when designing studies to collect new data, but also when evaluating the applicability of existing measurements as estimates of exposure concentrations in a new assessment. It is of particular concern when the measurement data will be used to extrapolate to long time periods, such as lifetimes. Transport and dispersion models are frequently used to help answer these questions (Calabrese & Kostecki, 1992).

The exposure assessor is likely to encounter several different types of measurements. One type often used to understand concentration trends is outdoor fixed-location monitoring. This measurement is used by the U.S. EPA and other groups to provide a record of pollutant concentration at one place over time. Nationwide air and water monitoring programs have been established so that baseline values in these environmental media can be documented. Although it is not practical to set up a national monitoring network to gather data for a particular exposure assessment, data from existing networks can be evaluated for relevance to an exposure assessment. These data are often far removed from the point of contact. Adapting data from previous studies usually presents specific challenges.

Indoor air contaminant concentrations can vary as much as or more than those in outdoor air (Wallace et al., 1985, 1986, 1987a, 1987b; Roberts et al., 1993). Consequently, indoor exposure is best represented by measurements taken at the point of contact. However, because pollutants such as carbon monoxide can exhibit substantial outdoor penetration, indoor exposure estimates should consider potential outdoor, as well as indoor, sources of the contaminant(s) under evaluation (U.S. EPA, 1992c; Ott & Roberts, 1998).

Contaminant concentrations in food and drinking-water measurements can also be measured. General characterization of these media, such as market basket studies (where representative diets are characterized), shelf studies (where foodstuffs are taken from store shelves and analyzed), or drinking-water quality surveys, are usually far removed from the point of contact for an individual, but may be useful in evaluating exposure concentrations for a large population. Measurements of tap water or foodstuffs in a home and how they are used are closer to the point of contact. In evaluating the relevance of data from previous studies, variation in the distribution systems must be considered, as well as the space-time proximity (U.S. EPA, 1992c).

Consumer or industrial product analysis is sometimes done to characterize the chemical concentrations in products. Product formulations can change substantially over time, similar products do not necessarily have similar formulations, and regional differences in product formulation can also occur. These should be considered when determining the relevance of existing data and when setting up sampling plans to gather new data (U.S. EPA, 1992c).

Another type of concentration measurement is the microenvironmental measurement. Rather than using measurements to characterize the entire medium, this approach defines specific zones in which the concentration in the medium of interest is thought to be relatively homogeneous, and then characterizes the concentration in that zone (U.S. EPA, 1992a; Price et al., 1998). Typical microenvironments include the home or parts of the home, office, automobile, or other indoor settings. Microenvironments can also be divided into time segments (e.g., kitchen during the day, kitchen during the night). This approach can produce measurements that are closely linked with the point of contact, both in location and time, especially when new data are generated for a particular exposure assessment. The more specific the microenvironment, however, the greater is the burden on the exposure assessor to establish that the measurements are representative of the population of interest.

The concentration measurement that provides the closest link to the actual point of contact is personal monitoring. In virtually all cases, if available, this information should be the basis of exposure assessments of individuals. An obvious exception is the work environment where lapel sampling is conducted while the person is wearing a respirator; in this case, personal sampling would not reflect genuine exposure.

Models and Their Role

Often the most critical element in an exposure assessment is estimating pollutant concentrations at exposure points. This is usually carried out by combining field data and modeling results. In the absence of field data, this process often relies on the results of mathematical models of aerial dispersion, such as ISCLT, or of water movement, such as MODFLOW (U.S. EPA, 1983–1989, 1985, 1986, 1987a; El Saadi & Langley, 1994). The U.S. EPA Science Advisory Board and others have recommended that modeling ideally should be linked with monitoring data in regulatory assessments, although this is not always possible.

A modeling strategy has several aspects, including setting objectives, model selection, obtaining and installing the code, calibrating and run-

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ning the computer model, and validation and verification. Many of these aspects are analogous to the quality assurance and quality control measures applied to measurements.

Regardless of whether models are extensively used in an assessment or whether a formal modeling strategy is documented in the exposure assessment plan, when computer simulation models such as fate and transport models and exposure models are used in exposure assessments, the assessor must be aware of the performance characteristics of the model and state how the exposure assessment requirements are satisfied by the model (Calabrese & Kostecki, 1992).

The site must be characterized if models are to be used to simulate pollutant behavior at a specific site. Site characterization for any modeling study includes examining all data on the site, such as source characterization, dimensions and topography of the site, location of receptor populations, meteorology, soils, geohydrology, and ranges and distributions of chemical concentrations. For exposure models that simulate both chemical concentration and time of exposure (through behavior patterns), data on these two parameters must be evaluated (U.S. EPA, 1992a; Paustenbach et al., 1991b, 1992b).

Criteria are provided by the U.S. EPA (1987a) for selecting surface water models and groundwater models, respectively; the reader is referred to this document for details. Similar selection criteria exist for air dispersion models.

A primary consideration in selecting a model is whether to perform a screening study or a detailed evaluation. A screening study makes a preliminary evaluation of a site or a general comparison between several sites. It may be generic to a type of site (i.e., an industrial segment or a climatic region) or may pertain to a specific site for which sufficient data are not available to properly characterize the site. Screening studies can help direct data collection at the site by, for example, providing an indication of the level of detection and quantification that would be required and the distances and directions from a point of release where chemical concentrations might be expected to be highest.

An example of a screening-level modeling effort would be to estimate the amount of lead deposited by an incinerator onto local crops using a basic air dispersion model, without considering local geographical or weather conditions. The next level of complexity would consider the presence of mountains, their proximity to the stack, the local weather patterns, and the number of atmospheric inversions per year. A higher level of analysis could incorporate yet other, more subtle factors.

The value of the screening-level analysis is that it is simple to perform and may indicate that no significant contamination exists. Screening-level models are frequently used to get a first approximation of the concentrations that may be present. Often these models use very conservative assumptions; that is, they tend to overpredict concentrations or exposures. If the results of the conservative screening procedure predict concentrations or exposures at less than a predetermined no-concern level, then more detailed analysis is

probably not necessary. If the screening estimates are above that level, refinement of the assumptions or a more sophisticated model are necessary to generate a more realistic estimate (U.S. EPA, 1992c).

Screening-level models also help the user conceptualize the physical system, identify important processes, and locate available data. The assumptions used in the preliminary analysis should represent conservative conditions, such that the predicted results overestimate potential conditions, limiting false negatives. If the limited field measurements or screening analyses indicate that a contamination problem may exist, then a detailed modeling study may be useful.

In contrast, the purpose of the detailed evaluation is to use the best data available to make the best estimate of spatial and temporal chemical distributions of a specific site. Detailed studies typically require higher quality data and more sophisticated models.

Accounting for Background Concentrations

Background exposure to so-called "toxic" or industrial chemicals, especially environmentally persistent ones, can occur due to natural or anthropogenic sources (Travis & Hester, 1990). In most exposure assessments, background soil concentrations are the focus of attention, but the same issue can be relevant when evaluating sediments, ambient air, groundwater, and vegetation (foodstuffs). At some sites, it is important that these so-called "background" concentrations be accounted for because removing the quantity of toxicant due to humans may, in fact, not appreciably change the concentrations or be sufficient to reduce the risk to acceptable levels. For example, naturally occurring concentrations of lead, arsenic, and cadmium, in some locations, may be higher than cleanup levels established by various regulatory agencies (Dragun & Chiasson, 1991; Dragun, 1998). The exposure assessor should try to determine local background concentrations by gathering data from nearby locations clearly unaffected by the site under investigation, or by referring to published works that have assessed this issue. Statistical approaches are applicable to address this issue (Ott, 1995a).

When assessing soils, background levels can be viewed in at least four different ways (El Saadi & Langley, 1994):

- "Pristine" levels—Some would like to equate background levels with those associated with the "pristine" state, that is, soils or landscapes unaffected by human activity. This rather idealistic situation probably no longer exists; even in Antarctica, where mercury and dioxin concentrations can be detected in some media. Toxic elements mainly associated with the solid phase of some natural material (such as soil dust, plant or volcanic ash, vegetable matter) are relatively mobile in a global sense. For example, Nriagu (1979) has suggested that about 40 million tons of heavy metals have been dispersed atmospherically over the many centuries of human activity.

  Increases in pollutant metal concentrations have been measured up to 60 km from smelters, and automotive lead (fine particles) has been

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measured in soils and rainfall up to about 50 km downwind from major cities. Soil contamination up to 50–100 m from highways by automotive lead (coarser particles) is an example of short-range transport, and contrasts with transport of toxic metals on a continental or global scale (e.g., contamination of the Greenland ice sheets from the northern United States, mercury in the Florida Everglades due to aerial releases in South America, the snows of the New Zealand Alps by soil dust from inland Australia) (El Saadi & Langley, 1994).

- "Normal" levels—The question could be asked: Are soils contaminated at farms in the higher rainfall areas of the Appalachians, which used to receive automotive exhaust particulates from the New York metropolitan area 200 km away? These soils are not pristine, but the chemical concentrations are perfectly safe for growing food, raising farm animals, and residential living. Soils from such areas would have a range of what is often called "normal" background values. To most exposure assessors, this mosaic of normal soils, which is only affected by the minor pollution of everyday activities associated with modern rural and urban life, should be the basis for defining background values. Statistically, this range of normal background values would constitute a single lognormally distributed population. Obviously, one needs to exclude the outliers or "hot" spots due to a geochemical anomaly, or localized pollution arising from either industrial emissions, disposal of waste products, or intensive (excessive) use of farm chemicals (El Saadi & Langley, 1994).
- Historically polluted regions—Local community and regulatory policies often affect what are defined as background levels. A community with highly developed environmental consciousness may insist on very low, possibly unreasonable, reference values. Some densely populated areas with historically derived pollution, perhaps from former mining activities, may sustain apparently healthy populations who pragmatically must accept higher "background" level values. The cities of Philadelphia, Baltimore, and New York, and parts of Japan, for example, may fit in this category.
- Geochemical variation—Background levels of some potentially toxic elements may vary among geographical regions because of differences in soil type. The resulting concentrations are often called naturally occurring levels.

  An important factor is the composition of rocks and sediments that weather from soils. Some extreme examples are high concentrations of nickel, cobalt, and chromium in igneous rocks such as basalts that cover extensive areas in western Victoria and Tasmania, Australia; and high concentrations of boron in soils on marine sediments in the Riverina, Mallee, and Wimmera districts of South Australia, and in Victoria, Eyre Peninsula and parts of western Australia.

Some regulatory agencies have provided written guidance describing how to select soil or sediment cleanup values that account for background chemical concentrations. In past years, these have varied significantly, but within the past 5 yr, there appears to be some convergence regarding the definition of background, how to measure it, and how it should affect exposure assessment calculations.

ESTIMATING UPTAKE VIA THE SKIN

When attempting to predict chemical risks in the environmental or occupational setting, the dermal exposure route can vary in its importance from negligible to significant. In most evaluations of hazardous waste sites and ambient air or water contaminants, this is not a major route of exposure. Although the uptake of chemicals via the skin has generally been overlooked in most workplace exposure assessments, it probably represents a substantial portion of the exposure for many occupations. Even though gloves are more frequently used than in years past and training has increased on the possible hazards of dermal exposure, there is still ample evidence to indicate that, in order to conduct a complete exposure assessment, this route deserves attention (Paustenbach et al., 1992c; Leung & Paustenbach, 1994; Paustenbach, 1988).

In addition to the risks associated with systemic toxicity due to uptake via the skin, it is sometimes necessary to evaluate the allergic contact dermatitis hazard (ACD). In recent years, techniques have been developed to quantitatively predict the likelihood of illication and induction of ACD (Nethercott et al., 1994; Jayjock, 1998). Some regulatory agencies are concerned with ACD and have developed cleanup standards based on this health endpoint.

In the workplace, a worker's skin frequently comes into contact with solvents or chemicals mixed in water (aqueous materials). In most environmental settings where persons can be exposed to contaminated soil or contaminated water, dermal uptake must be assessed. Fortunately, a good deal of research has been conducted to understand the rate at which chemicals pass through the skin. Percutaneous absorption of neat chemicals (i.e., the pure liquid) was often studied in humans until the late 1970s (Piotrowski, 1977; Stewart & Dodd, 1964; Dutkiewicz & Piotrowski, 1961; Dutkiewicz & Tyras, 1967; Feldmann & Maibach, 1974; Piotrowski, 1971; Mraz & Nohova, 1992; Krivanek et al., 1978). Because of the potential toxicity of many chemicals and improved laboratory techniques, in vivo human studies have been largely supplanted by experiments with laboratory animals, in vitro studies, or athymic rodents grafted with human skin (Klain & Black, 1990). Historical research has shown that, in general, chemical penetration of the human skin is similar to that of a pig or monkey, and much slower than that of the rat and rabbit (Bartek et al., 1972). Thus, for many chemicals, there is some level of confidence that the rate of dermal uptake of a chemical by humans can be inferred from animal data.

Starting in the 1980s, in vitro studies using human skin began to be conducted on a more routine basis. In these studies, a piece of excised

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skin is attached to a diffusion apparatus with a top chamber to hold the applied chemical and a temperature-controlled bottom chamber containing saline or other fluids (plus a sampling port to withdraw fractions for analysis) (Frantz, 1990). Although human forearm skin is optimal, it is difficult to obtain, so abdominal or breast skin is commonly used. Generally, a properly conducted in vitro test can be a reasonably good predictor of the absorption rate in vivo (Bronaugh et al., 1982). However, due to the fragile nature of the technique, these studies must be carefully interpreted (Barber et al., 1992). Often, depending on the conditions of the test, the results are not applicable to humans.

Aside from neat liquids and exposure to contaminated water, dermal exposures can also occur through contact with dust or dirt on surfaces, and by way of contact with soil or dust-bound contaminants (Paustenbach et al., 1997b). Few studies (Lepow et al., 1975; Roels et al., 1980; Que Hee et al., 1985; Driver et al., 1989; Sheppard & Evenden, 1994; Finley et al., 1994a; Holmes et al., 1996; Kissel et al., 1996b; Johnson & Kissel, 1996) have directly estimated soil loading on human skin, and only one of them attempted to measure dermal contact of contaminated equipment by workers (Marlow et al., 1990). The available studies probably provide sufficient data to generate point estimates of soil adherence and perhaps can provide a reasonable probability density function (PDF) for most persons exposed to contaminated soils. The degree of representativeness of the data to the general population is difficult to assess (Burmaster & Thompson, 1997).

Recently, a few of studies measured the adherence of soil to multiple skin surfaces (hands, forearms, lower legs, faces, and feet) under ambient and recreational conditions (Holmes et al., 1996; Kissel et al., 1996b). Dermal loading on the hands was found to vary over five orders of magnitude and to be dependent on the type of activity. Differences between pre- and postactivity adherence demonstrated the episodic nature of dermal contact with soil. However, due to the activity-dependent nature of soil exposure, data from these studies must be interpreted for their relevance to the type of activity, frequency, duration, and otherwise site-specific nature of exposure. The various studies involving contaminated soil are informative for providing an estimate of exposure; however, they are probably a couple orders of magnitude greater than what might be expected in an occupational setting. Nonetheless, this work is a "starting point" for bracketing potential exposure to dusts in the workplace.

Recently, there has been a reasonable level of research investigating exposure to house dust. The basis for this concern has been increasing evidence that controlling exposure to house dust, especially in homes located near sites with considerable surface soil contamination, is more important for reducing the health hazard than remediating the soil (Paustenbach et al., 1997b). Numerous papers in recent years have shown that in-house exposure to toxics is much greater than that encountered due to ambient (so-called environmental) contamination (Wallace, 1998; Ott & Roberts, 1998).

Along these lines, and of particular interest to those who study indoor exposure, is the recent work to develop standardized approaches for collecting wipe samples and estimating the amount of dust loading on the palm of the hand (Lioy et al., 1993, 1998). Although dermal absorption of toxicants in house dust will almost always pose a relatively low dermal uptake hazard, the uptake of toxicants due to hand-to-mouth contact can be substantial (Paustenbach et al., 1997b).

Quantitative Description of Dermal Absorption

For the purposes of risk assessment, percutaneous absorption is defined as transport of externally applied chemicals through cutaneous structures and the extracellular medium to the bloodstream (U.S. EPA, 1992a, 1999a). In many settings, such as for agricultural workers, platers, mechanics, and others, dermal uptake is the primary route of exposure. The simplest way to describe the rate of skin absorption is to apply Fick's first law of diffusion at steady state (Wepierre & Marty, 1979; Surber et al., 1990):

$$J = dQ/dt = DK\,\nabla C/e \approx k_p' C \qquad (3)$$

where J (= dQ/dt) is the chemical flux or rate of chemical absorbed (mg/cm^2-h), D is the diffusivity in the stratum corneum (cm^2/h), k the stratum corneum/vehicle partition coefficient of the chemical (unitless), ∇C the concentration gradient (mg/cm^3), e the thickness of the stratum corneum (cm), K_p the permeability coefficient (cm/h), and C the applied chemical concentration (mg/cm^3). The concentration gradient is equal to the difference between the concentration above and below the stratum corneum. Because the concentration below is small compared to the concentration above, ∇C can be approximated as equal to the applied chemical concentration. From the preceding equation, it can be seen that the rate of absorption is directly proportional to the applied concentration. The diffusivity represents the rate of migration of the chemical through the stratum corneum. Since the stratum corneum has a nonnegligible thickness, there is a period of transient diffusion (lag time), during which the transfer rate rises to reach a steady state. In these studies, the steady state is maintained indefinitely, provided the system remains constant. Depending on the type of chemical, the lag time can range from minutes to days (Leung & Paustenbach, 1994). From an exposure assessment standpoint, if the exposure duration is shorter than the lag time, it is unlikely that there will be any significant systemic absorption (Surber et al., 1990; Guy et al., 1982).

The partition coefficient (K_p) is one of the key parameters that influences the degree to which a chemical penetrates the skin (Surber et al., 1990; Guy et al., 1982; Gargas et al., 1989; Anderson et al., 1988; Flynn, 1990). Fatty chemicals tend to accumulate in the stratum corneum. Conversely, the stratum corneum is an effective barrier for hydrophilic substances, which tend to have low skin absorption rates. Because stratum

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corneum/vehicle partition coefficients are difficult to measure, the three parameters (D, k, and e) are combined to give an overall permeability coefficient (K_p). It is noteworthy that Eq. (3) only approximates most in vivo exposure situations in which true steady-state conditions are rarely attained. In spite of its limitations, this equation has yielded satisfactory estimations of the actual absorption rates of chemicals for many situations (Table 4).

Pharmacokinetic Models for Estimating the Uptake of Chemicals in Aqueous Solution

Pharmacokinetic models predict the uptake of a chemical through the skin based on fundamental thermodynamics. Several different models have been proposed. For example, a four-compartment pharmacokinetic model was developed in 1982 (Gargas et al., 1989). This model, which uses first-order rate constants, describes chemical movement through the compartments representing the various skin structures. It has been used successfully to predict the chemical disposition in the skin and plasma as a function of their physicochemical properties, and when an input rate constant to the skin surface is added to the model, it can be used to assess vehicle effects. A similar model that treats the barrier membrane as a series of spaces filled with immiscible liquids has also been developed (Anderson et al., 1988); its advantage is that it allows examination of non-steady-state conditions where Fick's law does not apply.

Under an infinite-dose situation where the amount of a chemical lost by penetration is too small to alter the applied concentration (e.g., where one is swimming), the rate of absorption is essentially linear once steady-state has been reached. In the finite-dose system, however, the chemical

TABLE 4. Human Cutaneous Permeability Coefficient Values for Some Industrial Chemicals in Aqueous Medium

	MW	K_{ow}	Observed	Calculated[a]
Organic chemicals				
2-Amino-4-nitrophenol	154.13	21.38	0.00066	0.019
4-Amino-2-nitrophenol	154.13	9.12	0.0028	0.0081
Aniline	93.12	7.94	0.041[b]	0.091
Benzene	78.11	134.90	0.11	0.39
p-Bromophenol	173.02	389.05	0.036	0.25
Butane-2,3-diol	90.12	0.12	<0.00005	0.0009
n-Butanol	74.12	7.59	0.0025	0.024
2-Butanone	72.10	1.94	0.0045	0.007
Carbon disulfide	76.14	100.	0.54[b]	0.3
Chlorocresol	142.58	1258.93	0.055	1.31
5-Chlorophenal	128.56	147.91	0.033	0.19
p-Chlorophenal	128.56	257.04	0.036	0.34
Chloroxylenal	156.61	1621.81	0.059	1.35
m-Cresol	108.13	100.	0.015	0.18
o-Cresol	108.13	100.	0.016	0.18
p-Cresol	108.13	85.11	0.018	0.15

TABLE 4. Human Cutaneous Permeability Coefficient Values for Some Industrial Chemicals in Aqueous Medium (*Continued*)

	MW	K_{ow}	Observed	Calculated[a]
Organic chemicals (*continued*)				
Decanol	158.28	37151.52	0.08	30.11
2,4-Dichlorophenol	163.01	1995.26	0.06	1.5
1,4-Dioxane	88.10	0.38	0.00043	0.0016
Ethanol	46.07	0.49	0.0008	0.0036
2-Ethoxyethanol	90.12	0.29	0.0003	0.0013
Ethylbenzene	106.16	1412.54	1.215[b]	2.65
Ethylether	74.12	6.76	0.016	0.022
p-Ethylphenol	122.17	549.54	0.035	0.79
Heptanol	116.20	257.04	0.038	0.41
Hexanol	102.17	102.15	0.028	0.21
Methanol	32.04	0.17	0.0016	0.0026
Methyl hydroxybenzoate	152.15	91.2	0.0091	0.082
β-Naphthol	144.16	691.83	0.028	0.7
3-Nitrophenol	139.11	100.00	0.0056	0.11
4-Nitrophenol	139.11	81.28	0.0056	0.09
Nitrosodiethanolamine	134.13	0.13	0.0000055	0.0005
Nonanol	144.26	2951.21	0.06	2.99
Octanol	130.22	933.25	0.061	1.19
Pentanol	88.15	36.31	0.006	0.091
Phenol	94.11	32.36	0.0082	0.074
Propanol	60.09	2.00	0.0017	0.0088
Resorcinol	110.11	6.03	0.00024	0.011
Styrene	104.14	891.25	0.635[b]	1.72
Thymol	150.21	1995.26	0.053	1.84
Toluene	92.13	489.78	1.01	1.15
2,4,6-Trichlorophenol	197.46	2344.23	0.059	1.02
3,4-Xylenol	122.16	169.82	0.036	0.25
Inorganic chemicals				
Cobalt chloride	129.84		0.0004	
Lead acetate	325.29		0.0000042[b]	
Mercuric chloride	271.50		0.00093	
Nickel chloride	129.60		0.001	
Nickel sulfate	154.75		<0.000009	
Silver nitrate	169.87		<0.00035[b]	
Sodium chromate	161.97		0.0021[b]	

Note. From Leung and Paustenbach (1994).

[a]Permeability coefficients calculated using equation presented in Leung and Paustenbach (1994).

[b]All the observed permeability coefficients were obtained by using in vitro techniques except those denoted with superscript *b*, which were determined in vivo.

solution is applied as a thin film and the concentration decreases as penetration proceeds (e.g., a splash). All other model parameters being the same, penetration is reduced under finite-dose conditions. This is because the chemical concentration is continuously reduced over time, resulting in a decrease in the gradient across the stratum corneum. These modeling

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results indicate that the mechanism by which fluxes are affected must be considered when extrapolating to non-steady-state conditions.

Although classic pharmacokinetic modeling like that described by Guy et al. (1982) can provide a good mathematical description of the disposition of chemicals, it does not depict exactly the biological processes in the intact animal. Fortunately, due to recent improvements in available computer hardware and software, pharmacokinetic methods based on physiological principles are now feasible alternatives for analysis of in vivo skin penetration studies. These so-called PBPK models realistically describe the disposition of the chemical in the intact animal in terms of rates of blood flow, permeability of membranes, and partitioning of chemicals into tissues (Andersen et al., 1991; Anderson et al., 1988). Characterizing dermal absorption in terms of actual anatomical, physiological, and biochemical parameters facilitates extrapolations to the real species of interest, humans.

In 1991, a PBPK model was developed to describe percutaneous absorption of volatile organic contaminants in dilute aqueous solutions (Shatkin & Brown, 1991). The exposure scenario modeled was either hand or full-body immersion into a vessel of solute-contaminated water. Modeling results suggested that chemical uptake in aqueous solutions is most markedly influenced by epidermal blood flow rates, followed by epidermal thickness and lipid content of the stratum corneum. In general, thicker and fattier skin provides a better barrier to dermal penetration of chemicals. These are precisely the principles under which barrier creams offer their protection for increasing the effective thickness and lipophilicity of the skin. This model also predicted that the dose of some volatile organic chemicals in water absorbed through the skin during a 20-min bath may be equivalent to the amount inhaled (Shatkin & Brown, 1991).

Among the most complex and best validated of the various models for dermal uptake of liquids is that developed by McDougal (1996). This team has successfully predicted dermal uptake rates for humans for more than a dozen chemicals based on animal data. One advantage of dermal PBPK models over traditional in vivo methods is their ability to accurately describe nonlinear biochemical and physical processes. For example, describing skin penetration based on blood concentrations or excretion rates as "percent absorbed" assumes that all processes have a simple linear relationship with the exposure concentration. This is often not the case. The kinetics become nonlinear when the absorption, distribution, metabolism, or elimination of a chemical is saturated at high exposure concentrations. This model and models developed since then address this phenomenon in a reasonable manner.

Factors Used to Estimate Dermal Uptake

Many factors that need to be quantitatively accounted for in order to estimate the likely systemic uptake of a chemical that comes into contact with the skin, either as a liquid or when present in soil or dust (Paustenbach et al., 1999; U.S. EPA, 1992b).

Dermal Bioavailability The typical media of concern for assessing cutaneous contact to environmental chemicals, in contrast with occupational exposure, are house dust, soil, fly ash, and sediment. In the workplace, dermal uptake is due to direct contact with liquids and contact with surfaces contaminated with dirt or liquids. A number of parameters can influence the degree of cutaneous bioavailability of chemicals in complex matrices. These may include aging (time following contamination), soil type (e.g., silt, clay, and sand), type and concentration of co-contaminants (e.g., oil and other organics), and the concentration of the chemical contaminant in the media (Shu et al., 1988). The bioavailability of a chemical in soil will usually be affected by its physicochemical properties. High-molecular-weight chemicals tend to bind to soil/dust and be less water soluble, while smaller molecules will frequently be water soluble, less tightly bound, and relatively bioavailable (McKone, 1990; Hrudey et al., 1996). The cutaneous bioavailability of perhaps 20 to 30 chemicals in soils has been determined in animals (Shu et al., 1988; Hrudey et al., 1996; Lucier et al., 1986; Umbreit et al., 1986a, 1986b; Skrowronski et al., 1988; Wester et al., 1993a). These studies show that different media and different chemicals can yield dramatically different cutaneous bioavailabilities. The results of these studies, for example, produce values of bioavailability for different chemicals that range from 0.001 to 3% for chemicals in soil.

Skin Surface Area There is an abundance of information about the surface area of different portions of the body. One simple approach is to use the "rule of nines" for estimating the surface area of the human body (Snyder, 1975): the head and neck are 9%, upper limbs are each 9%, lower limbs are each 18%, and the front or back of the trunk is 18% (Paustenbach, 1989). The U.S. EPA has estimated an exposed surface area (arms, hands, legs, and feet) of 2900 cm^2 for children 0 to 2 yr old; 3400 cm^2 for children 2 to 6 yr old; and 2940 cm^2 for adults (an adult is assumed to wear pants, an open-neck short-sleeve shirt, shoes, and no hat or gloves) (U.S. EPA, 1992c). When assessing chemical exposure in the ambient environment, most of the necessary surface area information can be found in the U.S. EPA *Exposure Factors Handbook* (U.S. EPA, 1997b). Table 5 presents the skin surface areas commonly used when conducting exposure assessments (Snyder, 1975). A distribution plot of skin area versus body weight has been developed (Burmaster, 1998b).

Soil Loading on the Skin A key factor to consider when estimating dermal uptake via soil is the soil-to-skin adherence rate. Values of 0.5 to 0.6 mg/cm^2 and 0.2 to 2.8 mg/cm^2 have been reported for adults and children, respectively (Paustenbach et al., 1986; Que Hee et al., 1985; California Department of Health Services, 1986; Driver et al., 1989). Recent works by Finley et al. (1994a), Kissel et al. (1996b), and Holmes et al. (1996) have built on prior studies to show that dermal loading can vary significantly among different activities and different people. Based on data collected in past studies, in 1992 the U.S. EPA suggested a default soil-to-

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TABLE 5. Representative Surface Areas of the Human Body (Adult Male)

Body portion	Area (cm^2)
Whole body	18,000
Head and neck	1,620
Head	1,260
Back of head	320
Neck	360
Back of neck	90
Torso	6,480
Back	2,520
Chest	2,520
Sides	1,440
Upper limbs	3,240
Upper arms (elbow–shoulder)	1,440
Lower arms (elbow–wrist)	1,080
Hands	720
Palms	360
Upper arms (back of)	360
Lower arms (back of)	270
Lower limbs	6,480
Thighs	3,240
Lower legs (knee–ankle)	2,160
Feet	1,080
Soles of feet	540
Thighs (back of)	810
Lower legs (back of)	540
Perineum	180

Note. Data adapted from Snyder (1975).

skin adherence rate of 0.2 mg/cm^2 (median) and 1.0 mg/cm^2 (95th percentile) for an adult. The recent edition of the *Exposure Factors Handbook* gives considerable attention to this topic (U.S. EPA, 1996c, 1996e). One approach to improving dermal uptake calculations is to use area-weighted adherence factors as recently suggested by the U.S. EPA.

Interpreting Wipe Samples

In some workplaces, wipe sampling has been conducted historically to assess the degree of surface contamination. Hospitals were among the first occupational settings, as long ago as 1940, to rely on this method to determine microbial levels in operating rooms. In pharmaceutical manufacturing, wipe sampling has been used as an indicator of hygienic conditions since the 1960s. The health physics profession has utilized wipe samples extensively as an indicator of the need for better housekeeping and decontamination; this group performed most of the early work in quantifying the relationship of wipe sample concentrations to dermal and oral uptake.

Over the years, few papers have discussed how to collect and interpret wipe samples (ECETOC, 1993a, 1993b; Caplan, 1993; McArthur, 1992; Kissel et al., 1996a; Fenske, 1993). When the primary effect of a chemical is skin discoloration, allergic contact dermatitis (ACD), or chloracne, wipe sampling was nearly always the preferred approach for assessing the acceptability of the workplace (rather than relying on air samples). Beginning in the 1980s, a substantial number of wipe samples were collected in office buildings contaminated with dioxins and furans after electrical transformer fires to estimate the potential human exposure (Michaud et al., 1994). The interpretation of these data was often mishandled and, as a result, a number of decisions by risk managers were less than optimal, resulting in significant unnecessary expenses. Today, better approaches are available.

Although wipe sampling data have generally been used as an indicator of cleanliness (Caplan, 1993), these data can also be used to estimate systemic uptake of a contaminant if the degree of skin contact with the contaminated surfaces is known. While historical wipe sampling methods were rather imprecise, they were useful for obtaining a rough estimate of the possible exposure, which could be refined later by other means, such as biological monitoring.

If one knows that wipe sampling results are representative of what comes into contact with the hands (i.e., actually able to be absorbed), then the procedures for converting wipe sample data to estimates of systemic uptake are straightforward (Brouwer & Van Hemmen, 1992). For example, if one knows the number of times a surface (e.g., valve handle, instrument controller, or drum) is touched, the surface area of the hand touching these items (usually the palm), and the percutaneous chemical absorption rate, then the uptake can be estimated using wipe sample information. The best wipe sampling data were those collected in a reliable and consistent manner, with a focus on the mass per unit area. Hand wash sampling is often more representative than wipe samples (Fenske & Lu, 1994).

Until recently, no standardized approaches existed for conducting wipe sampling. Differences in the use of wetting agent (acetone, methylene chloride, water, saline, isopropanol, and ethanol) and sampling media (paper, cotton, and synthetic fibers) produced drastically different results. In some procedures, especially those that used methylene chloride (in which the paint was concurrently stripped by the solvent), the chemical in the paint matrix was assumed to be bioavailable (a completely unreasonable assumption). Clearly, much of the previous work, which measured the amount of chemical released following aggressive scrubbing of the contaminated surfaces with detergent or solvent, did not reflect a realistic exposure scenario. Thus, there has been a need for standard techniques that attempt to mimic the conditions in which a hand comes into contact with a contaminated surface (McArthur, 1992). Some of the techniques have been developed by

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hygienists involved in agricultural exposure assessment (Knaak et al., 1989; Lavy et al., 1980, 1982; Popendorf & Leffingwell, 1982).

In an attempt to fill this need, fairly sophisticated work to standardize these procedures has been conducted by researchers at Rutgers University. In fact, some of their wipe sampling procedures and devices have been patented (Lioy et al., 1993). They have also developed a dry contact sampling device (Lioy et al., 1998) that offers promise for understanding the hazard from surface dusts. The implications from recent wipe sampling research are that: (1) a minimum number of samples is needed to have statistical confidence; (2) the pressure applied to the cloth during sample collection should be standardized; (3) neat solvent should not be used as a collection media; (4) the size of the sample area needs to be sufficient to collect enough contaminant for quantification; and (5) the technique should be validated by using glove analyses.

Estimating the Dermal Uptake of Chemicals in Soil

One of the most frequently occurring exposure scenarios involving environmental exposures is that of contaminated soil (Paustenbach et al., 1986). Unfortunately, dermal uptake of chemicals found on soil has rarely been evaluated experimentally (Leung & Paustenbach, 1994). A model to estimate the amount of an organic chemical in soil that crosses the stratum corneum into the underlying tissue layer has been developed (McKone, 1990). To differentiate this absorptive process from bioavailability, which also includes transport into blood, McKone refers to the percentage of available chemical as an uptake fraction. The approach is based on the fugacity concept, which measures the tendency of a chemical to move from one phase to another. Because the skin has a fat content of about 10% and soil has an organic carbon content on the order of 1 to 4%, an organic chemical in soil placed on the skin will move from the soil to the underlying adipose layers of the skin. However, this transfer depends on the period of time between deposition on the skin and removal by evaporative processes. The mass-transfer coefficients of the soil-to-skin layer and the soil-to-air layer define the rate at which these competing processes occur.

Results of this model suggest that the chemical uptake fraction in soil varies with the exposure duration, soil deposition rate, and physical properties of the chemical, and is particularly sensitive to the values of K_{ow}, as well as the mass or depth of soil deposited on the skin. When the amount of soil on the skin is low (<1 mg/cm^2), a high uptake fraction, approaching unity in some cases, is predicted. With higher soil loading (20 mg/cm^2), an uptake of only 0.5% is predicted. Because of the diverse variations of the uptake fraction with soil loading, results obtained from experiments with a single soil loading should be applied with caution to human soil-exposure scenarios.

The dermal uptake of chemicals in soil is a complex process, but its behavior is predictable if the controlling factors are accounted for and quantified (Leung & Paustenbach, 1994; McKone, 1990). In situations involving a relatively thin layer of a chemical on the skin for purposes of screening assessments, a few generalizations can be made. First, for chemicals with a high K_{ow} and a low air:water partition coefficient, it is reasonable to assume 100% uptake in 12 h. Second, for chemicals with an air:water partition coefficient greater than 0.01, the uptake fraction is unlikely to exceed 40% in 12 h. Third, for chemicals with an air:water partition coefficient greater than 0.1, one can expect less than 3% uptake in 12 h. In most occupational settings, contaminated soil will rarely be in contact with the skin for greater than 4 h before it is washed off. Consequently, this should be accounted for when attempting to predict systemic uptake.

Dermal Uptake of Chemicals in Soil

To estimate chemical uptake, one needs to know the percutaneous absorption rate, the exposed skin area, the chemical concentration, and the exposure duration. One scenario would be a thin film of chemical on the skin. For this finite-dose scenario, Eq. (5) is useful:

$$\text{Uptake (mg)} = (C)(A)(x)(f)(t) \quad (5)$$

where C is the concentration of the chemical (mg/cm^2), A the skin surface area (cm^2), x the thickness of the film layer (cm), f the absorption rate (percent per hour), and t the duration of exposure (h).

Another scenario would be an excess amount of a chemical on the skin (i.e., infinite dose). In this case, the thickness of the chemical layer is not calculated and steady-state kinetics are assumed. For a chemical in an aqueous or gaseous media:

$$\text{Uptake (mg)} = (C)(A)(K_p)(t)(d) \quad (6)$$

where d is the distribution factor.

For a neat liquid chemical,

$$\text{Uptake (mg)} = (A)(J)(t) \quad (7)$$

where K_p is the permeability coefficient (cm/h) and J the flux of chemical (mg/cm^2-h).

The U.S. EPA has suggested using the following equation for estimating percutaneous absorption of chemicals in soil (U.S. EPA, 1992b):

$$\text{Uptake (mg)} = (C)(A)(r)(B) \quad (8)$$

where C is the concentration of the chemical in soil (mg/g), A the skin surface area (cm^2), r the soil-to-skin adherence rate (g/cm^2), and B the cutaneous bioavailability (unitless).

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Example Calculation 3: Skin Uptake of a Chemical in Soil A person gardens with soil contaminated on average with 250 ng dioxin/soil (250 ppb). Assuming that the person's hands and lower arms are in contact with the soil, the soil loading is equal to 0.2 mg/cm², and the cutaneous bioavailability of dioxin in soil is 1% (Shu et al., 1988), what is the plausible uptake of dioxin by this person [using Eq. (8)]? Assume that the person washes his or her hands every 4 h and the exposed area of skin is 1800 cm².

$$\text{Uptake (ng)} = (C)(A)(r)(B)$$

where:

C = 250 ng/g
A = 1800 cm²
r = 0.2 mg/cm²
B = 0.01

By substitution:

$$\text{Uptake} = \left(\frac{250 \text{ ng TCDD}}{1 \text{ g soil}}\right)\left(\frac{0.2 \text{ mg soil}}{\text{cm}^2 \text{ skin}}\right)\left(\frac{1 \text{ g}}{10^3 \text{ mg}}\right)(1800 \text{ cm}^2 \text{ skin})(0.01)$$

$$= 0.9 \text{ ng TCDD}$$

Note: A preferred method for performing this calculation, if data are available, is to use a flux rate (ng/cm²-h) for the chemical. Assume that rate is 500 ng/cm²-h:

$$\text{Uptake (ng)} = (C)(f)(A)(t)$$

where

f = 500 ng/cm²-h
t = 4 h

By substitution:

$$\text{Update} = \left(\frac{250 \text{ ng TCDD}}{1 \text{ g soil}}\right)\left(\frac{1 \text{ g}}{10^9 \text{ ng}}\right)(1800 \text{ cm}^2 \text{ skin})(4\text{h})\left(\frac{500 \text{ ng}}{\text{cm}^2 - \text{h}}\right)$$

$$= 0.9 \text{ ng TCDD}$$

Uptake of Chemicals in an Aqueous Matrix

Published estimates of dermal uptake of chemicals in water have generally focused on evaluating workplace or environmental exposure. A number of different scenarios has been evaluated (Scow et al., 1979; Byard, 1989; Jo et al., 1988; Kerger & Paustenbach, 1997; Kezic et al., 1997). If interested in the possible uptake of a chemical present in water, the amount of chlordane absorbed through the skin by a man swimming for 4 h in water containing 1 ppb chloroform has been estimated (Jo et al., 1988). This is useful to compare various approaches. For example, the amount of chloroform absorbed by a boy swimming for 3 h in water has been calculated (Popendorf & Leffingwell, 1982). Some have compared the amounts absorbed through the skin during a 10-min shower versus a 20-min bath with water containing 1 ppb 1,1,1-trichlorethane (Kerger & Paustenbach, 2000).

About 10 yr ago, it was recognized that in the indoor environment, oral exposure to volatile chemicals present in drinking water may not necessarily represent the vast majority of the risk. Specifically, it was found that inhalation exposure due to the release of vapors from liquids to which people were in close contact could be relatively high. For example, comparisons have been made of the chloroform concentration in exhaled breath after a shower to that after an inhalation-only exposure (Jo et al., 1988). The concentration after showering was about twice that after the inhalation-only exposure, indicating that the absorbed dose from the skin is approximately equivalent to that from inhalation absorption.

Example Calculation 4: Skin Uptake of a Chemical From Water A person has filled his swimming pool with shallow well water contaminated with 0.002 mg/ml (2 ppb) toluene. What is the plausible dermal uptake of toluene while swimming in the contaminated water for half an hour? Assume that 18,000 cm² of skin is exposed and the K_p is 1.01 cm/h. From Eq. (6):

$$\text{Uptake} = (C)(A)(K_p)(t)(d)$$

where

C = 0.002 mg/ml
A = 18,000 cm²
K_p = 1.01 cm/h
t = 0.5 h
d = distribution factor (1 ml of water covers 1 cm³)

By substitution:

$$\text{Uptake} = (0.002 \text{ mg/ml})(18{,}000 \text{ cm}^2)(1.01 \text{ cm/h})(0.5 \text{ h})(1 \text{ ml water}/1 \text{ cm}^3)$$
$$= 18 \text{ mg}$$

Percutaneous Absorption of Liquid Solvents

While the percutaneous absorption of chemical solutes generally proceeds by simple diffusion, the skin uptake of neat chemical liquids is not necessarily exclusively governed by Fick's law. Consequently, the uptake of neat liquid through the skin needs to be estimated using direct in vivo skin contact techniques. Table 6 presents the percutaneous absorption rates

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TABLE 6. Absorption Rates of Some Neat Industrial Liquid Chemicals in Human Skin In Vivo

Chemical	Absorption rate (mg/cm²-h)
Aniline	0.2–0.7
Benzene	0.24–0.4
2-Butoxyethanol	0.05–0.68
2-(2-Butoxyethoxy)ethanol	0.035
Carbon disulfide	9.7
Dimethylformamide	9.4
Ethylbenzene	22–23
2-Ethoxyethanol	0.796
2-(2-Ethyoxyethoxy)ethanol	0.125
Methanol	11.5
2-Methoxyethanol	2.82
2-(2-Methoxyethoxy)ethanol	0.206
Methyl butyl ketone	0.25–0.48
Nitrobenzene	2
Styrene	9–15
Toluene	14–23
Xylene (mixed)	4.5–9.6
m-Xylene	0.12–0.15

Note. From Leung and Paustenbach (1994).

of some neat industrial liquid solvents that have been determined in human volunteer studies.

Example Calculation 5: Skin Uptake of a Neat Liquid Chemical Due to carelessness or a leak, the inside of a glove becomes contaminated with 2-methoxyethanol. How much can be absorbed if a worker wears the contaminated glove on one hand for half an hour? Assume the surface area of exposed skin is 360 cm^2 and the flux rate is 2.82 mg/cm^2-h. From Eq. (7),

$$\text{Uptake} = (A)(J)(t)$$

where

$$A = 360\ cm^2$$
$$J = 2.82\ mg/cm^2\text{-h}$$
$$t = 0.5\ h$$

By substitution,

$$\text{Uptake} = (360\ cm^2)(2.82\ mg/cm^2\text{-h})(0.5\ h)$$
$$= 508\ mg$$

To understand the relative hazard from skin exposure versus inhalation exposure, the dose of 2-methoxyethanol absorbed by the same worker

via inhalation for 8 h (10 m^3 of air inhaled), assuming a threshold limit value (TLV) of 16 mg/cm^3, can be estimated and compared to the dose due to inhalation exposure. Assume an 80% inhalation uptake efficiency.

$$\text{Inhalation uptake} = (16\ mg/m^3)(10\ m^3)(0.8)$$
$$= 128\ mg$$

Thus, the uptake of 2-methoxyethanol following 30 min of skin exposure of a single hand can be as much as 4 times that from inhalation for 8 h at the TLV concentration, a presumably safe level of exposure. From this example, it is clear that the cutaneous route of entry can, in some situations, significantly contribute to the total absorbed dose, especially in the occupational setting.

Percutaneous Absorption of Chemicals in the Vapor Phase

Until the 1990s, it was generally assumed that the plausible dose resulting from vapors absorbed through the skin was too low to pose a hazard. Only a few studies have examined this issue (Krivanek et al., 1978; Kezic et al., 1997; U.S. EPA, 1999a). A few clinical reports have encouraged some limited in vivo research to evaluate the absorption of several chemicals in the gaseous phase through the human skin (Table 7). A chamber system to measure the whole-body percutaneous absorption of chemical vapors in rats has been described by McDougal et al. (1990), and this approach has produced some interesting results (Mattie et al., 1994). In

TABLE 7. Percutaneous Absorption Rates for Chemical Vapors In Vivo

Chemical	Skin uptake in combined exposure (%)[a]	Permeability coefficient K_p (cm/h)	
		Rat	Human
Styrene	9.4	1.75	0.35–1.42
m-Xylene	3.9	0.72	0.24–0.26
Toluene	3.7	0.72	0.18
Perchloroethylene	3.5	0.67	0.17
Benzene	0.8	0.15	0.08
Halothane	0.2	0.05	
Hexane	0.1	0.03	
Isoflurane	0.1	0.03	
Methylene chloride		0.28	
Dibromomethane		1.32	
Bromochloromethane		0.79	
Phenol			15.74–17.59
Nitrobenzene			11.1
1,1,1-Trichloroethane			0.01

Note. Rat data from McDougal et al. (1990).

[a] In combined exposure, rats are simultaneously absorbing chemical vapors by inhalation and by whole-body absorption through the skin.

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this system, chemical flux across the skin is determined from the chemical concentration in blood during exposure by using a PBPK model. In most cases, vapor absorption through the skin amounts to less than 10% of the total dose received from a combined skin and inhalation exposure. While there is good agreement between the rat and human in the relative ranking of the permeability coefficients among the chemicals studied, for an individual chemical the rat skin appears to be two to four times more permeable than the human skin. These observations are consistent with previously reported data (Piotrowski, 1971, 1977; Shu et al., 1988; Bronaugh et al., 1982; Barber et al., 1992).

It is generally not necessary to account for the contribution from percutaneous uptake of vapors when the occupational exposure limit (OEL) is used as a guideline for acceptable exposure, because uptake of vapors through the skin is usually inherent in the data; that is, the studies of animals or humans from which data were collected were usually exposed via inhalation (whole body) so dermal uptake of the vapor occurred. However, although good work practices and the law require that situations where persons are placed in atmospheres that are life-threatening, were it not for a supplied air respirator, not occur, sometimes in emergency situations, airline (supplied air) respirators or self-contained breathing apparatus (SCBA) are worn in environments containing chemical concentrations 10-fold to 1000-fold greater than the TLV. In these cases, it is important to account for vapor uptake through either exposed or covered skin.

Although nearly all data on vapor absorption involve bare skin, the role of clothing in preventing skin uptake has occasionally been evaluated. For example, a study of workers wearing denim clothing indicated no decreased uptake of phenol vapors (Piotrowski, 1971), but found a 20% and 40% reduction in uptake of nitrobenzene (Piotrowski, 1967) and aniline vapors, respectively (Dutkiewicz & Piotrowski, 1961). Although standard clothing may slightly decrease the amount of a chemical transferred from air through the skin, it can be a significant source of continuous exposure if the clothing has been contaminated.

Example Calculation 6: Skin Uptake of a Chemical Vapor Assume that a person needs to repair a leaking pump, so he enters a room wearing an airline respirator. Assume the room contains 500 mg/m^3 nitrobenzene (100 times the current TLV) and it takes 30 min to repair the pump. How much nitrobenzene might be absorbed through the skin?

The head, neck, and upper limbs are assumed to be exposed (surface area = 4860 cm^2), and the rest of the body (surface area = 13,140 cm^2) is covered with clothing. Assume the percutaneous K_p of nitrobenzene is 11.1 cm/h, and that the clothing has reduced the skin uptake rate of vapors by about 20% (Piotrowski, 1967). From Example 5.

$$\text{Uptake} = (C)(A)(K_p)(t)$$

$$\text{Uptake through exposed skin} = (500\ \text{mg/m}^3)(4860\ \text{cm}^2)(11.1\ \text{cm/h}) \times (0.5\ \text{h})(1\ \text{m}^3/10^6\ \text{cm}^3)$$

$$= 13.5\ \text{mg}$$

$$\text{Uptake through clothing} = (500\ \text{mg/m}^3)(13{,}140\ \text{cm}^2)(11.1\ \text{cm/h}) \times (0.8)(0.5\ \text{h})(1\ \text{m}^3/10^6\ \text{cm}^3)$$

$$= 29\ \text{mg}$$

$$\text{Total uptake} = 13.5 + 29 = 42.5\ \text{mg}$$

From this example, it is clear that if one enters an environment containing a high concentration of an airborne contaminant, even if a supplied-air respirator is worn, the degree of skin uptake of the vapor may be worthy of evaluation to ensure that the worker is protected. These kinds of calculations sometimes have to be conducted in difficult work environments that are in a state of alert (e.g., submarines, chemical plants during emergency situations, etc.).

ESTIMATING INTAKE VIA INGESTION

If the appropriate information is available, estimating the intake of various chemicals due to ingestion is a relatively straightforward exercise. In general, one is concerned with the ingestion of the following media: drinking water, other liquids, food, soil, and house dust. Drinking-water contamination may occur because of soil contamination from leaking underground storage tanks, landfills, or hazardous waste sites, as well as discharges from contaminated streams or water transport systems. Nearly all foods in Western society contain a number of intentional and unintentional chemicals, including pesticide residues, naturally occurring chemicals, and food additives that serve as preservatives or enhancers of taste or visual appeal. Soils are ingested as a result of eating incompletely washed vegetables, hand-to-mouth contact, and through direct ingestion by children. Soils are also ingested when particles too large to reach the lower respiratory tract are inhaled (and then are swallowed). House dust contaminated with a number of chemicals can be ingested due to contact with foods and hand-to-mouth activities (Paustenbach et al., 1997).

Estimating Intake of Chemicals in Drinking Water

Estimating the magnitude of the potential dose of toxics from drinking water requires knowledge of the amount of water ingested, the chemical concentrations in the water, and the chemical bioavailability in the gastroin-

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testinal tract. The amount of water ingested per day varies with each person and is usually related to the amount of physical activity. A good deal of literature has addressed the amount of water ingested by persons engaged in different kinds of activities (U.S. EPA, 1983–1989, 1985, 1997b).

Currently, the U.S. EPA suggests that when little is known about the specifics of exposure, a value of 2 L/d for adults and 1 L/d for infants (body weight of less than 10 kg) should be used as the default value. These rates include drinking water consumed in the form of juices and other beverages.

Numerous studies cited in the U.S. EPA *Exposure Factors Handbook* (U.S. EPA, 1996d, 1996e) have generated data on drinking-water intake rates. In general, these sources support the U.S. EPA use of 2 L/d for adults and 1 L/d for children as upper percentile tap-water intake rates. Many of the studies have reported fluid intake rates for both total fluids and tap water. Total fluid intake is defined as consumption of all types of fluids including tap water, milk, soft drinks, alcoholic beverages, and water intrinsic to purchased foods. Total tap water is defined as water consumed directly from the tap as a beverage or used to prepare foods and beverages (i.e., coffee, tea, frozen juices, soups, etc.). Data for both consumption categories are presented in numerous publications. Table 8 presents typical information reported from these studies (U.S. EPA, 1992c).

All currently available studies on drinking water intake are based on short-term survey data. Although short-term data may be suitable for obtaining mean intake values that are representative of both short- and long-term consumption patterns, upper percentile values may be different for short-term and long-term data because there is generally more variability in short-term surveys. It should also be noted that most of the currently available drinking water surveys are based on recall. This may be a source of uncertainty in the estimated intake rates because of the subjective nature of this type of survey technique (U.S. EPA, 1992c).

TABLE 8. Summary of Tap-Water Intake by Age

	Intake (ml/d)		Intake (ml/kg-d)	
Age group	Mean	10th–90th Percentiles	Mean	10th–90th Percentiles
Infants (<1 yr)	302	0–649	43.5	0–100
Children (1–10 yr)	736	286–1,294	35.5	12.5–64.4
Teens (11–19 yr)	965	353–1,701	18.2	6.5–32.3
Adults (20–64 yr)	1,366	559–2,268	19.9	8.0–33.7
Adults (65+ yr)	1,459	751–2,287	21.8	10.9–34.7
All ages	1,193	424–2,092	22.6	8.2–39.8

Note. From Ershow and Cantor (1989).

To estimate the intake of toxics via direct ingestion of drinking water, the calculation is straightforward:

$$\text{Intake} = (V)(C)(B)$$

where V is the volume of water (L/d), C the concentration of chemical in water (μg/L), and B the bioavailability (unitless).

One of the more interesting observations of the past 15 yr is that ingestion of contaminated drinking water is sometimes not the primary route of exposure to the toxicant in drinking water. Uptake of volatile chemicals via inhalation can be nearly as great in some homes as ingestion, which is the result of the presence of these chemicals in air due to showering, off-gases from the dishwasher, and other opportunities for volatilization of the chemical (Jo et al., 1988; Kerger & Paustenbach, 2000; Kezic et al., 1997; U.S. EPA, 1999a; Mattie et al., 1994).

The Importance of Soil Ingestion When Estimating Human Exposure

Between 1980 and 1995, predicted risks associated with the ingestion of contaminated soil were the primary drivers for remediating many (if not most) hazardous waste sites. As discussed by Paustenbach et al. (1986), there was no better example than the site in Times Beach, MO. Hundreds of millions of dollars can be needed to clean up these kinds of sites to levels that would not pose a significant risk if children actually ate significant quantities of contaminated soil. Because of the expense of remediation, a good deal of research has been conducted over the past 15 yr to attempt to quantitatively understand this route of exposure.

Clearly, the ingestion of soil and house dust is a potential source of human exposure to toxicants (Roberts & Dickey, 1995; Roberts et al., 1992, 1993). The potential for contaminant exposure via this source is greater for children because they are more likely to ingest greater quantities of soil than adults. Inadvertent soil ingestion among children may occur through the mouthing of objects or hands. Mouthing behavior is considered to be a normal phase of childhood development. Adults may also ingest soil or dust particles that adhere to food, cigarettes, or their hands. Deliberate soil ingestion is defined as pica and is considered to be relatively uncommon. Because normal, inadvertent soil ingestion is more prevalent and data for individuals with pica behavior are limited, the focus of most exposure assessments is on normal levels of soil ingestion that occur as a result of mouthing or unintentional hand-to-mouth activity (U.S. EPA, 1992c; Paustenbach et al., 1986; Copeland et al., 1993; Kimbrough et al., 1984).

Mouthing activities by children, which are generally accepted as normal and commonplace (e.g., Barltrop (1966) estimated that almost 80% of all children at age 1 yr exhibited mouthing tendencies), are potential exposure routes to trace amounts of soil and/or dust adhering to fingers,

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hands, and objects placed in the mouth. The available data indicate that soil exposure occurs through several indirect routes:

1. Soil contributes to house dust (e.g., by local dust deposition, and mud and dirt carried in by shoes and pets, etc.).
2. House dust (fine particles) adheres to objects and to children's hands.
3. Children ingest dust particles when sucking and mouthing objects and fingers.

Obviously, in some situations, exposure may be direct (a child playing outdoors may eat dirt directly). In other situations, oral exposure to chemicals in soil may occur via contamination of domestic water supplies or contamination of fruit and vegetable produce grown onsite. However, the content and concentration of dusts in the indoor environment, which may represent the most important source of indirect exposure to soil, need to be better understood (Paustenbach et al., 1997b; El Saadi & Langley, 1994).

Many studies have been conducted to estimate the amount of soil ingested by children. Most of the early studies attempted to quantify the amount of soil ingested by measuring the amount of dirt present on children's hands and making generalizations based on behavior. More recently, soil intake studies have been conducted using a methodology that measures trace elements in feces and soil that are believed to be poorly absorbed in the gut. These measurements are used to estimate the amount of soil ingested over a specified period of time.

Studies of Soil Ingestion

In light of the importance of soil ingestion for estimating human exposure to contaminated soil, several literature surveys have been undertaken to identify the typical amount of soil consumed by children and adults (U.S. EPA, 1992c, 1996c; Paustenbach et al., 1986; El Saadi & Langley, 1994; Kimbrough et al., 1984). Research evaluating lead uptake by children from ingestion of contaminated soil, paint chips, dust, and plaster provides the best source of information. Walter et al. (1980) estimated that a normal child typically ingests very small quantities of dust or dirt between the ages of 0 to 2 yr, the largest quantities between 2 to 7 yr, and nearly insignificant amounts thereafter. In the classic text by Cooper (1957), it was noted that the desire of children to eat dirt or place inedible objects in their mouths becomes established in the second year of life and disappears more or less spontaneously by the age of 4 to 5 yr. A study by Charney et al. (1980) also indicated that mouthing tends to begin at about 18 mo and continues through 72 mo, depending on several factors such as nutritional and economic status, as well as race. Work by Sayre et al. (1974) indicated that ages 2 to 6 yr are the important years, but that "intensive mouthing diminishes after 2 to 3 years of age."

An important distinction that is often blurred is the difference between the ingestion of very small quantities of dirt due to mouthing tendencies and the disease known as pica. Children who intentionally eat large quantities of dirt, plaster, or paint chips (1 to 10 g/d), and consequently are at greater risk of developing health problems, can be said to suffer from the disease known as pica. This disease is known as geophagia if the craving is for dirt alone. Geophagia, rather than pica, is generally of greatest concern in areas with contaminated soil.

Duggan and Williams (1977) have summarized the literature on the amount of lead ingested through dust and dirt. In their opinion, a quantity of 50 µg of lead was the best estimate for daily ingestion of dust by children. Assuming, on the high side, an average lead concentration of 1000 ppm would indicate a soil and dust ingestion rate of 50 mg/d. Lepow et al. (1974) estimated an ingestion rate equal to 100 to 250 mg/d (specifically, 10 mg ingested 10 to 25 times a day). Barltrop (1966) and Barltrop et al. (1975) also estimated that the potential uptake of soils and dusts by a toddler is about 100 mg/d. In a Dutch study, the amount of lead on hands ranged from 4 to 12 ng. By assuming maximum lead concentrations of 500 µg/g (concentrations were typically lower) and complete ingestion of the contents adsorbed to a child's hand on 10 separate occasions, the amount of ingested dirt would equal 240 mg. Thus, in order to eat 10,000 mg soil/d, the rate once suggested by the Center for Disease Control (Kimbrough et al., 1984), children would have to place their hands into their mouths 410 times a day, a rate that seems improbable (National Research Council, 1974; Paustenbach, 1987).

A report by the National Research Council (1974) addressing the hazards of lead suggested a rate of 40 mg/d. Day et al. (1975) measured the amount of dirt transferred from children's hands (age range from 1 to 3 yr) to a sticky sweet, and estimated a daily intake of 2 to 20 sweets would lead to dirt intake of 10 to 1000 mg/d. Bryce-Smith (1974) estimated 33 mg/d. In its document addressing lead in air, the U.S. EPA assumed that children ate 50 mg/d of household dust, 40 mg/d of street dust, and 10 mg/d of dust derived from their parents' clothing (i.e., a total of 100 mg/d).

Kimbrough et al. (1984) used a series of assumptions about soil exposure when estimating the possible risks of contaminated soil at Times Beach, MO, based upon unpublished observations about children's behavior and hand-mouth activity. A few years later, Kimbrough noted that their estimate of up to 10,000 mg/d was clearly an exaggeration and her personal estimate would be nearer 50 mg/d (El Saadi & Langley, 1994).

La Goy (1987) based his soil ingestion estimates upon a review of the literature, in particular using empirical data derived by Binder et al. (1986) and Van Wijnen et al. (1990). Similarly, Paustenbach et al. (1992b) based their estimates upon a review of the literature, including the mass-balance quantitative study conducted by Calabrese et al. (1989).

De Silva (1991, 1994) adopted a different approach that may overcome some of the uncertainties inherent in the assumptions of the above

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indirect studies. She applied a "slope factor" increase of 0.6 μg/dl in children's blood lead levels for each 1000 ppm increase in soil lead [this factor was developed by Barltrop et al. (1975) following his work on blood lead levels in children from villages on old mining sites]. De Silva then deduced that an increase of 0.6 μg/dl in blood indicates an extra oral intake of 3.75 μg lead/d, based upon a U.S. EPA (1986) calculation that an increase of 1.0 μg lead/d in children's diets produces an increase of 0.16 in the blood lead level. With a soil lead value of 1000 ppm, 3.75 mg soil would contain 3.75 μg lead, suggesting that 3.75 mg/d (say 4 mg) of soil was ingested by the children. However, the slope factor used here may not be the most appropriate, since mining soil wastes typically have larger sized particles, which tends to decrease lead bioavailability compared with soil contaminated by lead smelter activity, and therefore reduces the slope factor.

A major step forward beyond estimating soil ingestion using indirect measurements was the attempt to study tracer elements found in soil with elements measured in the urine and feces of children. Several studies have been conducted thus far that have used this approach (Binder et al., 1986; Calabrese et al., 1989, 1990, 1996; de Silva, 1991, 1994; Stanek & Calabrese, 1991; Calabrese & Stanek, 1991; Stanek & Calabrese, 1995a, 1995b, 1995c). In one early tracer study, evaluated the amount of soil eaten by 24 hospitalized and nursery-school children. They analyzed the amount of aluminum, titanium, and acid-soluble residue in the feces of children aged 2 to 4 yr. The data were normally distributed. They found an average of 105 mg/d of soil in the feces of nursery children, and 49 mg/d in hospitalized children. Even with the limited number of children in the study, the difference between the two groups was significant ($p < .01$). If the value for the hospitalized children is assumed to be the background level because these substances are taken in from nonsoil sources (e.g., diet and toothpastes), the estimated average amount of soil ingested by the nursery school children would be 56 mg/d. This value is in the lower range of estimates in the literature and supports the use of 100 mg/d as a conservative uptake of soil by toddlers (ages 2 to 4 yr).

There have been two major studies completed by Calabrese et al. (1989, 1990, 1996; Stanek & Calabrese, 1991; Calabrese & Stanek, 1991; Calabrese et al., 1997; Calabrese & Stanek, 1998; Stanek et al., 1997). In the first, they quantitatively evaluated 6 different tracer elements in the stools of 65 school children aged 2 to 4 yr. They attempted to evaluate children from diverse socioeconomic backgrounds. This study, conducted in Massachusetts, was more definitive than prior investigations because they analyzed the children's diets, assayed for the presence of tracers in the diapers, assayed house dust and surrounding soil, and corrected for the pharmacokinetics of the tracer materials.

In the second study, soil ingestion estimates were obtained from a stratified, simple random sample of 64 children aged 1–4 years residing

on a superfund site in Montana. The study was conducted during the month of September for 7 consecutive days (Calabrese et al., 1997). Soil ingestion was estimated by each soil tracer via traditional methods as well as by an improved approach using five trace elements (Al, Si, Ti, Y, and Zr), called the Best Tracer Method (BTM), which substantially corrects for error due to misalignment of tracer input and output as well as error occurring from ingestion of tracers from nonfood, nonsoil sources, while being insensitive to the particle size of the soil/dust ingested. According to the BTM, the median soil ingestion was less than 1 mg/day while the upper 95% was 160 mg/day. No significant age (1 year vs. 2, vs. 3) or sex-related differences in soil ingestion were observed. These estimates are lower than estimates observed in the first study, which was conducted in New England during September and October.

Based on the series of papers by Calabrese et al. (Calabrese et al., 1989, 1990, 1996; Stanek & Calabrese, 1991; Calabrese & Stanek, 1991, 1998), a few generalizations can be made. These studies were difficult to conduct and interpret. Second, only children from a single climate were studied, and it can be expected that rates vary with the amount of time spent indoors and outdoors. Third, only a handful of children have been studied (less than 500), so it is not possible to characterize the percentage of children who might tend to ingest large quantities of soil or house dust. Fourth, the relevant amount of soil or house dust ingested indoors versus outdoors is not known yet. In most cases, the contaminant concentrations in dust can be quite different when found in a carpet versus the yard (Paustenbach et al., 1997b). Fifth, although there is some degree of uncertainty in the results of the various studies, it appears that a best estimate of soil intake for most children resides in the area of 10 to 25 mg/d. It appears that perhaps 1 to 5% of the children may ingest much larger amounts during certain days or weeks (e.g., 2000 mg/d), but these tendencies do not occur on a chronic basis.

The issue of how much soil and house dust children eat, as well as the percent of children who are engaged in these activities, has been an active area of research. These researchers have proposed that one can estimate uptake over the period of one year and they have proposed lifetime values (Stanek & Calabrese, 1995a). Recent work by Calabrese and Stanek (1998) suggests that prior work yielded reasonable results for purposes of risk assessment. Most of the values discussed here are presented in Table 9. As discussed previously, another area of research impacting exposure assessments of contaminated soil, which has been and continues to be actively pursued, is the bioavailability of the contaminant in the soil matrix (Hrudey et al., 1996).

What is the Significance of Pica?

There appears to be some confusion in the literature over what constitutes "pica." Pica can be defined as "the habitual ingestion of substances not normally regarded as edible," but some authors have included mouthing

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TABLE 9. Values for Childhood and Adult Soil Ingestion Rates That Have Been Used in Health Risk Assessments Conducted Between 1984 and 2000

Author	Age	Soil and dust (mg/d)
Barltrop (1973)	2–6 yr	100
Lepow et al. (1974)	2–6 yr	100–250
Day et al. (1975)	2–6 yr	10–1000
Kimbrough et al. (1984) (CDC)	0–9 mo	0
	9–18 mo	1000
	1.5–3.5 yr	10,000
	3.5–5 yr	1000
	5+ yr	100
Hawley (1985)	0–2 yr	Negligible
	2–6 yr	90
	6–18 yr	21
	18–70 yr	57
La Goy (1987)	1–6 yr	500 (max.)
	1–6 yr	100 (ave.)
Calabrese et al. (1989)	1–4 yr	27–85 (mean)
		9–16 (median)
Paustenbach (1991b)	2–4 yr	25–50
	Adults	2–5
De Silva (1994)	Children	~4
U.S. EPA (1997b)	Children	200
Calabrese & Stanek (1998)	Children	30–60 (best estimate)

and sucking activities in their definitions (e.g., Lourie & Cayman, 1963). Others appear to assume that all children with pica necessarily must be habitual soil eaters. In fact, pica behavior may be generalized to the ingestion of many different (nonfood) substances, or may be specific to one substance such as paper, soap, or earth. It is likely that repetitive pica behavior specifically for dirt, or habitual "geophagia," rarely occurs in the general population in most industrialized countries (Taylor, 1983; Danford, 1982).

Pica should, therefore, be considered a "normal" temporary phenomenon in some children. In the general population, the prevalence of both mouthing and pica, and the range of articles ingested, has been shown to decrease with age (Barltrop, 1966). In the 1-yr-old age group, 78% of children mouthed objects and 35% ingested them; this behavior decreased at the age of 4 yr, when 33% were mouthing and only 6% had pica.

It is also relevant to note that in certain circumstances, pica for soil may be culturally determined (such as eating clay, high in silicon and aluminum, for its medicinal properties in the relief of stomach discomfort and diarrhea by some Aborigines; or the custom of eating earth during pregnancy in certain cultures) (El Saadi & Langley, 1994). For example, some women in the southern portions of the United States report a craving for and eat certain clays during pregnancy.

Pica may be associated with physical disorders, including iron deficiency. However, it has been debated whether pica represents a cause or an effect of these deficiencies. Pica can also be associated with mental illness. It has also been reported that 25% of institutionalized mentally handicapped adults indulged in pica of one kind or another (including bizarre objects ranging from rags and string to rocks, insects, and feces) (Danford, 1982).

Calabrese and Stanek (1998) have indicated that in their studies, they have observed great variability in soil ingestion by children. They have noted, for example, that some children are highly variable in their soil ingestion activities, displaying little propensity for soil ingestion on one day while ingesting copious amounts the next day. While there has not been any concerted focus on the soil pica child, the available data indicate that some children ingest over 50 g of soil on particular days. They note that while it is true that some children will ingest large amounts of soil, it is far from certain whether soil pica is behavior that only a small subgroup displays over a limited number of years (e.g., one to six) or whether most children, on occasion, display this behavior or some combination of both behavioral patterns. Clearly, additional work is needed to understand this topic.

Soil Ingestion by Adults

For most persons beyond the ages of 5 to 6 yr, the daily uptake of dirt due to intentional ingestion is generally thought to be quite low. With the exception of some lower income persons who eat clays due to tradition or mineral deficiency, adults will not usually intentionally ingest dirt or soil. However, there are two other important ways in which adults eat dirt—incidental hand-to-mouth contact and through dust on vegetables. It has been shown that most soil ingested from crops comes from leafy vegetables. Interestingly, investigations at nuclear weapons trials have shown that particles exceeding 45 μm are seldom retained on leaves. Further, superficial contamination by smaller particles is readily lost from leaves, usually by mechanical processes or rain, and certainly by washing (Russell, 1966). As a result, unless the soil contaminant is absorbed into the plant, superficial contamination of plants by dirt will rarely present a health hazard (Martin, 1964; Paustenbach et al., 1986).

The estimated deposition rate of dust from ambient air in rural environments is about 0.012 μg/cm^2-d, assuming that rural dust contains about 300 μg/g of lead (the substance for which these data were obtained). The U.S. EPA has estimated that even at very high air concentrations (0.45 mg/m^3 total dust), it is unlikely that surface deposition alone can account for more than 0.6 to 1.5 μg lead/g dust (2 to 5 μg/g lettuce) on the surface of lettuce during a 21-d growing period (Paustenbach et al., 1986). These data suggest that daily ingestion of dirt and dust by adults due to eating vegetables is unlikely to exceed about 0 to 5 mg/d even if all of the 137 g of

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leafy and root vegetables, sweet corn, and potatoes consumed by adult males each day were replaced by family garden products.

In its document on lead, the U.S. EPA used worst-case assumptions to estimate that persons could ingest up to 100 μg of lead each day due to unwashed vegetables. The actual uptake by adults from vegetables should actually be much less, and is probably negligible, because the U.S. EPA estimate assumed that all of the suspended dust is contaminated; persons do not wash the vegetables; garden vegetables are eaten throughout the year, rather than only during the growing season; and persons actually replace most vegetables with their own garden products.

With respect to the second route—incidental ingestion—only a very limited amount of work has been conducted which addresses dust ingestion via this route. It has been suggested that the primary route of uptake will be through accidental ingestion of dirt on the hands, which may be of special concern to smokers, who tend to have more frequent hand-to-mouth contact. It is true that before the importance of this route of entry was recognized, persons who worked in lead factories between 1890 and 1920 probably received a large portion of their body burden of lead due to poor hygiene and ingestion of dust; however, such conditions are now rare in the United States and most developed countries.

Some persons have evaluated the exposure experience of agricultural workers who apply or work with pesticide dusts. Due to the frequency and degree of pesticide exposure during its manufacture or application, these data do not appear to be appropriate surrogates for estimating soil uptake from the hands of persons who live on or near sites having contaminated soil. In addition, most of the published studies on pesticides involve liquids such as the organophosphates, rather than "soil-like" particles. Exposure studies of persons who apply granular pesticides might be more useful for defining upper bound estimates of dermal exposure than estimates based on dusty workplaces (Knarr et al., 1985).

At least one study has been conducted to specifically address soil uptake by adults involved in remediating waste sites (Proctor et al., 1997; Stanek & Calabrese, 1995c; Calabrese & Stanek, 1998; also see Zartarian et al., 1998). The results suggest that the amount of soil eaten by these workers is much less than the default value of 100 mg/d suggested by the U.S. EPA in a number of guidance documents and risk assessments. Based on all the available data, it appears that a value of 5–25 mg/day for soil ingestion by most adults is a reasonable one.

Estimating the Intake of Chemicals Via Food

Without question, the information necessary to accurately estimate the ingestion of xenobiotics via foods is one the most complex of all exposure calculations. The hundreds of different possible foods and dozens of different chemicals that can be present as a pesticide residue, coupled with the background concentrations of various chemicals in soil, make this a formidable task.

The methodology for estimating uptake via ingestion must account for the quantity of food ingested each day, the concentration of contaminant in the ingested material, and the bioavailability of the contaminant in the media. Over the past 20 yr, a significant amount of work has been directed at understanding these exposure factors. Specifically, an entire volume of the U.S. EPA *Exposure Factors Handbook* (Volume II) is devoted to this topic (U.S. EPA, 1997b).

The approach to estimating uptake via foods was first applied in the late 1940s by the Food and Drug Administration (U.S. Department of Agriculture [USDA], 1972) and had not changed appreciably through 2000. However, because of the passage of the Food Quality Protection Act of 1996 (FQPA), the methodology for estimating uptake of chemicals from foods will be changing dramatically over the next 5–10 yr. Specifically, the FQPA requires that all pesticide residues from foods be added together, in a prescribed manner based on target organ, with the goal of understanding the total daily dose of all residual pesticides in the diet. Then, if necessary, the pesticide manufacturers are expected to calculate the necessary residue level that their chemical may have in a particular food so that the total dose does not exceed a fraction of the acceptable daily intake (ADI). Since there are hundreds of foods and dozens of residues, this presents a formidable challenge.

Ingestion of contaminated fruits and vegetables is a potential pathway of human exposure to chemicals. Fruits and vegetables may become contaminated by several different pathways. Ambient air pollutants may be deposited on or absorbed by plants, or dissolved in rainfall or irrigation waters that contact the plants. Plant roots may also absorb pollutants from contaminated soil and groundwater. The addition of pesticides, soil additives, and fertilizers may also result in food contamination (U.S. EPA, 1997b). Formulas are available to predict the concentration of chemicals from the soil, which have deposited from the air, and remain after treatment with a pesticide.

The primary information source on consumption rates of fruits and vegetables among the U.S. population is the U.S. Department of Agriculture (USDA) Nationwide Food Consumption Survey (NFCS) and the USDA Continuing Survey of Food Intakes by Individuals (CSFII). Data from the NFCS have been used in various studies to generate consumer-only and per-capita intake rates for individual fruits and vegetables, as well as total fruits and total vegetables. CSFII data from the 1989–1991 survey have been analyzed by the U.S. EPA to generate per-capita intake rates for various food items and food groups (U.S. EPA, 1984, 1997b; USDA, 1980).

Consumer-only intake is defined as the quantity of fruits and vegetables consumed by individuals who ate these food items during the survey period.

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Per-capita intake rates are generated by averaging consumer-only intakes over the entire population of users and nonusers. In general, per-capita intake rates are appropriate for use in exposure assessment for which average dose estimates for the general population are of interest, because they represent both individuals who ate the foods during the survey period and individuals who may eat the food items at some time but did not consume them during the survey period. Total fruit intake refers to the sum of all fruits consumed in a day, including canned, dried, frozen, and fresh fruits. Likewise, total vegetable intake refers to the sum of all vegetables consumed in a day, including canned, dried, frozen, and fresh vegetables.

Intake rates may be presented on either an as-consumed or a dry-weight basis. As-consumed intake rates (g/d) are based on the weight of food in the form in which it is consumed. In contrast, dry-weight intake rates are based on the weight of food consumed after the moisture content has been removed. In calculating exposures based on ingestion, the unit of weight used to measure the contaminant concentration in the produce will vary. Intake data from the individual NFCS and CSFII components are based on "as eaten" (i.e., cooked or prepared) forms of the food items or groups. Thus, no corrections are required to account for changes in portion sizes from cooking losses (USDA, 1992; Pao et al., 1982).

Estimating source-specific exposures to chemicals in fruits and vegetables may also require information on the amount of fruits and vegetables exposed to or protected from contamination as a result of cultivation practices, the physical nature of the food product itself (i.e., those having protective coverings that are removed before eating would be considered protected), or the amount grown beneath the soil (i.e., most root crops such as potatoes). The percentages of foods grown above and below ground will be useful when the contaminant concentrations in foods are estimated from concentrations in soil, water, and air. For example, vegetables grown below ground would more likely be contaminated by soil pollutants, but leafy above-ground vegetables would more likely be contaminated by deposition of air pollutants on plant surfaces. Some examples of various exposure factors and confidence ratings for liquids and food are presented in Table 10 (U.S. EPA, 1997b).

Individual average daily intake rates calculated from NFCS and CSFII data are based on averages of reported individual intakes over 1 d or 3 consecutive days. Such short-term data are marginally suitable for estimating mean average daily intake rates representative of both short-term and long-term consumption. However, the distribution of average daily intake rates generated using short-term data (e.g., 3 day) does not necessarily reflect the long-term distribution of average daily intake rates. The distributions generated from short-term and long-term data will differ to the extent that each individual's intake varies from day to day; the distributions will be similar to the extent that individuals' intakes are constant from day to day (U.S. EPA, 1997b).

TABLE 10. Summary of Default Exposure Factor Recommendations and Confidence Ratings for Citizens of United States

Exposure factor	Recommendation	Confidence rating
Drinking water intake rate	21 ml/kg-d or 1.4 L/d (average)	Medium
	34 ml/kg-d or 2.3 L/d (90th percentile)	Medium
	Percentiles and distribution also included	
	Means and percentiles also included for pregnant and lactating women	
Total fruit intake rate	3.4 g/kg-d (per capita average)	Medium
	12.4 g/kg-d (per capita 95th percentile)	Low
	Percentiles also included	
	Means presented for individual fruits	
Total vegetable intake rate	4.3 g/kg-d (per capita average)	Medium
	10 g/kg-d (per capita 95th percentile)	Low
	Percentiles also included	
	Means presented for individual vegetables	
Total meat intake rate	2.1 g/kg-d (per capita average)	Medium
	5.1 g/kg-d (per capita 95th percentile)	Low
	Percentiles also included	
	Percentiles also presented for individual meats	
Total dairy intake rate	8.0 kg-d (per capita average)	Medium
	29.7 g/kg-d (per capita 95th percentile)	Low
	Percentiles also included	
	Means presented for individual dairy products	
Grain intake	4.1 g/kg-d (per capita average)	High
	10.8 g/kg-d (per capita 95th percentile)	Low in long-term upper percentiles
	Percentiles also included	
Breast-milk intake rate	742 ml/d (average)	Medium
	1,033 ml/d (upper percentile)	Medium
Fish intake rate	General population	
	20.1 g/d (total fish) average	High
	14.1 g/d (marine) average	High
	6.0 g/d (freshwater/estuarine) average	High
	63 g/d (total fish) 95th percentile long-term	Medium
	Percentiles also included	
	Serving size	
	129 g (average)	High
	326 g (95th percentile)	High
	Recreational marine anglers	
	2–7 g/d (finfish only)	Medium
	Recreational freshwater	
	8 g/d (average)	Medium
	25 g/d (95th percentile)	Medium
	Native American subsistence population	
	70 g/d (average)	Medium
	170 g/d (95th percentile)	Low

Note. From U.S. EPA (1997a).

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Day-to-day intake variation among individuals will be greatest for food items or groups that are highly seasonal, and for items or groups that are eaten year-round but are not typically eaten every day. For these foods, the intake distribution generated from short-term data will not reflect long-term distribution. On the other hand, for broad categories of foods (e.g., vegetables), which are eaten on a daily basis throughout the year with minimal seasonality, the short-term distribution may be a reasonable approximation of the true long-term distribution, although it will show somewhat more variability.

Other relevant fruits and vegetables intake studies include the U.S. EPA Dietary Risk Evaluation System (DRES), Office of Pesticide Programs (OPP). The OPP uses the DRES (formerly the Tolerance Assessment System) to assess the dietary risk of pesticide use as part of the pesticide registration process (USDA, 1992; Pao et al., 1982). The OPP sets tolerances for specific pesticides on raw agricultural commodities based on estimates of dietary risk. These estimates are calculated using pesticide residue data for the food item of concern and relevant consumption data. Intake rates are based primarily on the USDA 1977–1978 NFCS, although intake rates for some food items are based on estimations from production volumes or other data (i.e., some items were assigned an arbitrary value of 0.000001 g/kg-d) (U.S. EPA, 1997b). The OPP has calculated per-capita intake rates of individual fruits and vegetables for 22 subgroups of the population (age, regional, and seasonal) by determining the composition of NFCS food items and disaggregating complex food dishes into their component raw agricultural commodities (RACs) (U.S. EPA, 1997b; White et al., 1983).

The advantage of using these data is that complex food dishes have been disaggregated to provide intake rates for a very large number of fruits and vegetables. These data are also based on the individual body weights of the respondents. Therefore, using these data to calculate chemical exposure may provide more representative estimates of potential dose per unit body weight. However, because the data are based on the NFCS short-term dietary recall, the same limitations discussed previously for other NFCS data sets also apply here. In addition, consumption patterns may have changed since the data were collected in 1977–1978. The OPP is in the process of translating consumption information from the USDA CSFII 1989–1991 survey to be used in DRES (U.S. EPA, 1997b).

The USDA has also conducted a study entitled *Food and Nutrient Intakes of Individuals in One Day in the U.S.* (U.S. EPA, 1997b; USDA, 1980). The USDA calculated mean intake rates for total fruits and total vegetables using NFCS data from 1977–1978 and 1987–1988, and CSFII data from 1994–1995 (U.S. EPA, 1997b; USDA, 1980). Mean per-capita total intake rates are based on intake data for 1 d from the 1977–1978 and 1987–1988 USDA NFCS, respectively. Data from both surveys are presented in the *Exposure Factors Handbook* to demonstrate that although the 1987–1988 survey had fewer respondents, the mean per-capita intake

rates for all individuals agree with the earlier survey. Also, slightly different age classifications were used in the two surveys, providing a wider range of age categories from which exposure assessors may select appropriate intake rates. The age groups used in this data set are the same as those used in the 1987–1988 NFCS. Information for per-capita intake rates and consumer-only intake rates for various ages of individuals is also available. Intake rates for consumers-only were calculated by dividing the per-capita consumption rate by the fraction of the population using vegetables or fruits in a day (U.S. EPA, 1997b).

The advantages of using these data are that they provide intake estimates for all fruits, all vegetables, or all fats combined. Again, these estimates are based on 1-d dietary data which may not reflect usual consumption patterns (U.S. EPA, 1997b).

Intake of Fish and Shellfish

Contaminated finfish and shellfish are potential sources of human exposure to persistent chemicals and metals. Pollutants are carried in surface waters, but also may be stored and accumulated in sediments as a result of complex physical and chemical processes. Consequently, various aquatic species can be exposed to pollutants and may become sources of contaminated food (U.S. EPA, 1997b).

Accurately estimating exposure to various chemicals in a population that consumes fish from a polluted water body requires an estimation of caught-fish intake rates by fishermen and their families. Commercially caught fish are marketed widely, making the prediction of an individual's consumption from a particular commercial source difficult. Because the catch of recreational and subsistence fishermen is generally not diluted in this way, these individuals and their families represent the population that is most vulnerable to exposure by intake of contaminated fish from a specific location (U.S. EPA, 1997b).

Over the years, fish consumption survey data have been collected using a number of different approaches, which need to be considered when interpreting the survey results. Generally, surveys are either "creel" studies in which fishermen are interviewed while fishing, or broader population surveys (using mailed questionnaires or phone interviews). Both data types can be useful for exposure assessment purposes, but somewhat different applications and interpretations are needed. In fact, creel study results have often been misinterpreted because of inadequate knowledge of survey principles (U.S. EPA, 1997b; Puffer et al., 1981; Price et al., 1994).

The typical survey seeks to draw inferences about a larger population from a smaller sample of that population. The larger population from which the survey sample is taken and to which the survey results are generalized describes the target population of the survey. In order to generalize from the sample to the target population, the probability of being sampled must be known for each member of the target population. This probability is

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reflected in weights assigned to each survey respondent, with weights being inversely proportional to sampling probability. When all members of the target population have the same probability of being sampled, all weights can be set to 1 and essentially ignored (Ruffle et al., 1994; Ebert et al., 1993).

In a mail or phone study of licensed anglers, the target population generally involves all licensed anglers in a particular area, and in these studies, the sampling probability is essentially equal for all target population members. In a creel study, the target population is anyone who fishes at the locations being studied; generally in a creel study, the probability of being sampled is not the same for all members of the target population. For instance, if the survey is conducted for 1 d at a site, then it will include all persons who fish there daily, but only about 1/7 of the people who fish there weekly, 1/30 of the people who fish there monthly, etc. In this example, the probability of being sampled (or inverse weight) is seen to be proportional to the frequency of fishing. However, if the survey involves interviewers who revisit the same site on multiple days, and persons who are only interviewed once for the survey, then the probability of being in the survey is not proportional to frequency; in fact, it increases less proportionally with greater frequency of fishing. If the same site is surveyed every day of the survey period with no reinterviewing, all members of the target population would have the same probability of being sampled, regardless of fishing frequency, implying that the survey weights should all equal 1 (Ebert et al., 1993; Roseberry & Burmaster, 1991).

On the other hand, if the survey protocol calls for individuals to be interviewed each time an interviewer encounters them (i.e., without regard to whether they were previously interviewed), then the inverse weights will again be proportional to fishing frequency, no matter how many times interviewers revisit the same site. Note that when individuals can be interviewed multiple times, the results of each interview are included as separate records in the database, and the survey weights should be inversely proportional to the expected number of times that an individual's interviews are included in the database (U.S. EPA, 1997b; Ebert et al., 1993; Roseberry & Burmaster, 1991).

Fish and shellfish exposure assessments are among the most complicated of all assessments (Murray & Burmaster, 1994). A significant portion of the *Exposure Factors Handbook* addresses this topic (U.S. EPA, 1997b). Recently, fairly complex Monte Carlo methods have been applied to resolve many of the difficulties estimating exposure of anglers and their families (Wilson et al., 2000).

Aggregate Exposure and FQPA

Pesticides are regulated under both the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetics Act (FFDCA). In 1996, Congress passed the Food Quality Protection Act (FQPA) that amended both FIFRA and FFDCA. These laws mandated the U.S. EPA

to register pesticides and set tolerances based on a safety determination, a reasonable certainty that use of a given pesticide or consumption of raw agricultural commodity of processed foods that contain the pesticide and its residues will cause no harm to human health or the environment. The U.S. EPA evaluates risks posed by the use and usage of each pesticide to make a determination of safety. Based upon this determination, the agency regulates pesticides to ensure that use of the chemical is not unsafe.

In the past, the U.S. EPA evaluated the safety of pesticides based on a single-chemical, single-exposure-pathway scenario. However, FQPA requires that the agency consider aggregate exposure in its decision-making process. Section 408(a)(4)(b)(2)(ii) of FFDCA specifies with respect to a tolerance that there must be a determination "that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." Section (b)(2)(C)(ii)(I) states that "there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residues" *Aggregate dose* is defined as the amount of a single substance available for interaction with metabolic processes or biologically significant receptors from multiple routes of exposure. *Aggregate risk* is defined as the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a single substance. Conversely, *cumulative risk* is defined as the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a group of substances sharing a common mechanism of toxicity.

As shown in Figure 5, the most basic concept underlying all aggregate exposure assessments is that exposure occurs to an individual. The integrity of the data concerning this exposed individual must be maintained throughout the aggregate exposure assessment. In other words, each of the individual "subassessments" must be linked back to the same person (U.S. FDA, 1998). Because exposures are based on that received by a single individual, aggregate exposure assessments must agree in time, place, and demographic characteristics. Each of these parameters have imbedded attributes that must be matched to create a reasonable assessment. Some of these imbedded attributes include:

- Time (duration, daily, seasonally).
- Place (location and type of home, urbanization, watersheds, region).
- Demographics (age, gender, reproductive status, ethnicity, personal preference).

To develop realistic aggregate exposure and risk assessments requires that the appropriate temporal, spatial, and demographic exposure factors be correctly assigned. Examples of some of these factors include sex- and age-specific body weights, regional specific drinking-water concentrations

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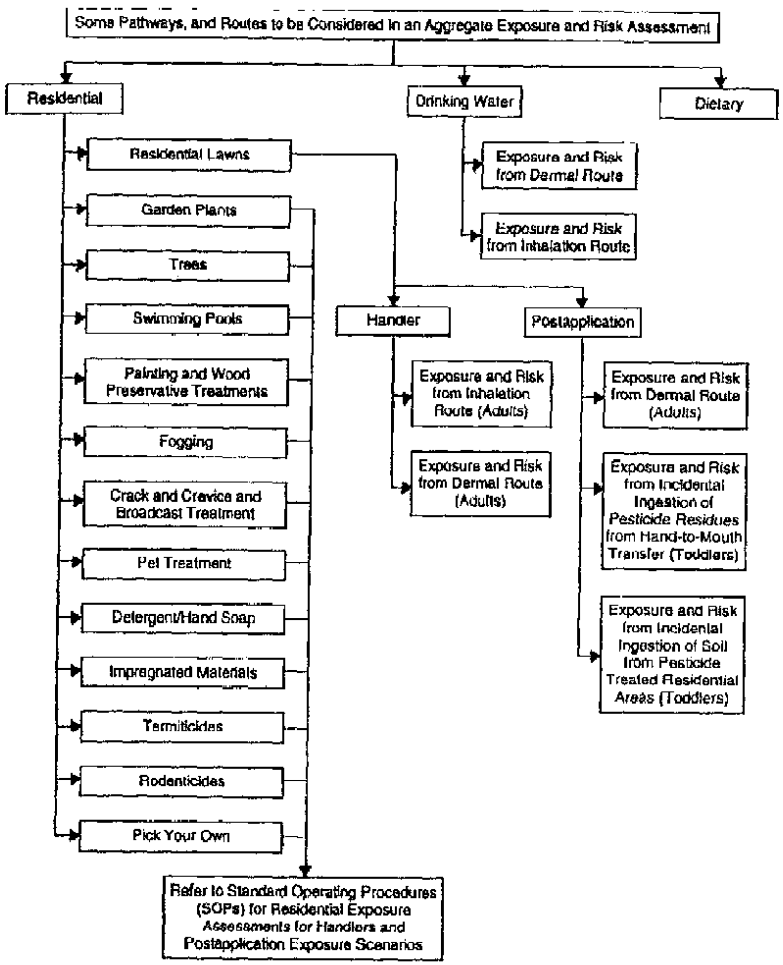
Some Pathways, and Routes to be Considered in an Aggregate Exposure and Risk Assessment
Residential
Drinking Water
Dietary
Residential Lawns
Garden Plants
Trees
Swimming Pools
Painting and Wood Preservative Treatments
Fogging
Crack and Crevice and Broadcast Treatment
Pet Treatment
Detergent/Hand Soap
Impregnated Materials
Termiticides
Rodenticides
Pick Your Own
Exposure and Risk from Dermal Route
Exposure and Risk from Inhalation Route
Handler
Postapplication
Exposure and Risk from Inhalation Route (Adults)
Exposure and Risk from Dermal Route (Adults)
Exposure and Risk from Dermal Route (Adults)
Exposure and Risk from Incidental Ingestion of Pesticide Residues from Hand-to-Mouth Transfer (Toddlers)
Exposure and Risk from Incidental Ingestion of Soil from Pesticide Treated Residential Areas (Toddlers)
Refer to Standard Operating Procedures (SOPs) for Residential Exposure Assessments for Handlers and Postapplication Exposure Scenarios

FIGURE 5. Factors to consider in an aggregate exposure assessment of a pesticide. *Source:* U.S. Environmental Protection Agency (1999). *Guidance for performing aggregate exposure and risk assessments* (Draft). Washington, DC.

of the pesticide being considered, seasonally based pesticide residues in food, and frequency of residential pest control representative of housing type. Once an aggregate exposure and risk assessment is completed for one individual, population and subpopulation distributions of exposures and risk may be constructed by probabilistic techniques (ILSI, 1998).

An aggregate exposure and risk assessment is distinct from a cumulative risk assessment. Cumulative risk is defined as "the measure or estimate of distributions of exposures (doses) for a set of chemicals that act by a common mechanism of toxicity" (U.S. EPA, 1998). Cumulative risk assessment evaluates risks from multiple chemicals via all routes and pathways of exposure. The cumulative risk assessment considers the combined toxicological effect of a group of chemicals with a common mechanism of toxicity. The definition of a common mechanism of toxicity is "two or more pesticide chemicals that produce an adverse effect(s) to human health by the same, or essentially the same, sequence of major biochemical events. The underlying basis of the toxicity is the same, or essentially the same, for each chemical" (U.S. EPA, 1998). Specific guidance concerning conducting a cumulative risk assessment is currently being developed (ILSI, 1998).

Breast Milk

Breast milk is a potential source of exposure to toxic substances for nursing infants. Lipid-soluble chemical compounds accumulate in body fat and may be transferred to breastfed infants in the lipid portion of breast milk. Because nursing infants obtain most (if not all) of their dietary intake from breast milk, they are especially vulnerable to exposures to these compounds. In fact, some models predict that the peak body burdens of certain chemicals (like dioxin) can reach their lifetime peak (μg/kg) on the last day of nursing at age 12–24 mo. Estimating the magnitude of the potential dose to infants from breast milk and that resulting body burdens of blood levels is quite complicated. It requires information on the quantity of breast milk consumed per day and the duration (months) over which breastfeeding occurs. Information on the fat content of breast milk is also needed for estimating dose from breast-milk residue concentrations that have been indexed to lipid content (U.S. EPA, 1997b; Smith, 1987). Until recently, these were considered the key parameters but it is now clear that one must account for the quickly increasing body weight of the infant, the differences in the blood perfusion of the fat compartments in the infant versus the mother, and other factors (Kerger et al., 1999; Kreuzer et al., 1997).

Several studies have generated data on breast-milk intake (Smith, 1994; Kohler et al., 1984; NAS, 1991; Neville et al., 1988). Typically, breast-milk intake has been measured over a 24-h period by weighing the infant before and after each feeding without changing its clothing (test weighing). The sum of the difference between the measured weights over the 24-h period is assumed to be equivalent to the amount of breast milk consumed daily. Intakes measured using this procedure are often corrected for evaporative water losses (insensible water losses) between infant weighings (NAS, 1991). Neville et al. (1988) evaluated the validity of the test-weight approach among bottle-fed infants by comparing the weight of milk taken from bottles with the difference between the before and after feeding

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weights of infants. Once corrected for insensible water loss, test-weight data were not significantly different from bottle weights. Conversions between weight and volume of breast milk consumed are made using the density of human milk (approximately 1.03 g/ml) (NAS, 1991). Recently, techniques for measuring breast-milk intake using stable isotopes have been developed; however, few data based on this new technique have been published (NAS, 1991).

Studies among nursing mothers in industrialized countries have shown that infant intake averages approximately 750 to 800 g/d (728 to 777 ml/d) during the first 4 to 5 mo of life, with a range of 450 to 1200 g/d (437 to 1165 ml/d) (U.S. EPA, 1997b; NAS, 1991). Similar intakes have also been reported for developing countries (U.S. EPA, 1997b; NAS, 1991). Infant birth weight and nursing frequency have been shown to influence the rate of intake (U.S. EPA, 1997b; NAS, 1991). Infants who are larger at birth and/or nurse more frequently have been shown to have higher intake rates. Also, breast-milk production among nursing mothers has been reported to be somewhat higher than the amount actually consumed by the infant (U.S. EPA, 1997b; Ebert et al., 1993).

Like exposure assessments of fishes, techniques for estimating chemical uptake by children of breast milk continue to evolve. One of the more interesting papers on this topic was recently presented by Kerger et al. (1999), which put into question most of the prior calculation approaches for estimating dose to nursing infants based, in part, on work conducted by Kreuzer et al. (1997). A portion of the U.S. EPA *Exposure Factors Handbook* addresses this topic, and a few published papers have offered some novel approaches (U.S. EPA, 1997b, 1997c; Smith, 1987). Some examples of breast-milk intake rates are presented in Table 11. A distribution for breast-milk consumption has been suggested by Kerger et al. (1999).

TABLE 11. Default Values for Daily Intakes of Breast Milk

Age	Number of infants surveyed at each time period	Mean intake (ml/d)	Range of daily intake (ml/d)
Completely breast-fed			
1 mo	11	600 ± 159	426–989
3 mo	2	833	645–1000
6 mo	1	682	616–786
Partially breast-fed			
1 mo	4	485 ± 79	398–655
3 mo	11	467 ± 100	242–698
6 mo	6	395 ± 175	147–684
9 mo	3	<554	451–732

Note. From Pao et al. (1982). Data expressed as mean ± standard deviation.

ESTIMATING UPTAKE VIA INHALATION

Estimating intake via inhalation depends on only a few exposure factors, such as inhalation rate; airborne chemical concentration; bioavailability, and, if it is a particle, particle size. In general, uncertainty in estimates of intake via inhalation is among the smallest for all exposure calculations.

Inhalation rates are known to vary directly with the amount of physical activity of the persons being evaluated. The default value used by the U.S. EPA and others is 20 m^3/d. When conducting occupational exposure assessments, it is common to assume that workers inhale about 10 m^3 in an 8-h workday (U.S. EPA, 1992c).

Airborne chemical concentrations are obtained through either direct measurement or modeling. The form of the chemicals in the air will be a gas (includes vapors) or particles (dusts or fumes). Generally, it is assumed that virtually all of the vapors or gases will be absorbed if inhaled (U.S. EPA, 1992c; Andelman, 1985; Krivanek et al., 1978). This may not be the case for volatile chemicals, if the concentration in the blood is approaching steady state. In those cases, a significant fraction of the inhaled vapors will be present in the exhaled breath and, therefore, not absorbed (Piotrowski, 1977).

It is usually assumed that if particles enter the lower respiratory tract, they will eventually be absorbed unless the chemical is highly insoluble. Generally, it is assumed that particles less than 150 μm in diameter are inhalable, but virtually all particles greater than 10 μm will be captured in the upper respiratory tract (nose and throat) and then ingested. It has often been assumed that particles less than 10 μm in diameter will be captured in the lower respiratory tract and the majority of these (by mass rather than particle number) will eventually be absorbed. Notably, for some chemicals, the adverse effect is related to the particle size, so this must be taken into account. For example, it is thought that beryllium particles should be collected in several different size fractions and that the severity of the adverse effect varies according to particle size.

Various Inhalation Rates

A significant amount of research has been done to correlate various inhalation rates with different tasks and body weights. Most studies on this subject have been summarized in the most recent U.S. EPA *Exposure Factors Handbook* (U.S. EPA, 1996c). Data are available for dozens of different levels of physical activity and the distributions for several populations are presented.

A number of equations have been proposed for predicting the inhalation rate based on body weight (U.S. EPA, 1997b). The *Exposure Factors Handbook* and other sources provide a number of tables that relate physical activity with inhalation rate (see Table 12).

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TABLE 12. Daily Inhalation Rates Estimated From Daily Activities

Subject	Inhalation rate (IR)		Daily inhalation rate (DIR)*
	Resting (m³/h)	Light activity (m³/h)	(m³/d)
Adult man	0.45	1.2	22.8
Adult woman	0.36	1.14	21.1
Child (10 yr)	0.29	0.78	14.8
Infant (1 yr)	0.09	0.25	5.76
Newborn	0.03	0.09	0.78

Note. From Snyder (1985). Assumptions made were based on 8 h resting and 16 h light activity for adults and children (10 yr); 14 h resting and 10 h light activity for infants (1 yr); 23 h resting and 1 h light activity for newborns.

$$^{a}\text{DIR} = \frac{1}{T}\sum_{i=1}^{k} \text{IR}_i t_i$$

where IR_i is corresponding inhalation rate at ith activity, t_i is hours spent during the ith activity, k is number of activity periods, and T is total time of the exposure period (i.e., a day).

Bioavailability of Airborne Chemicals

Because the mass of particles inhaled is usually quite small, and because most particles less than 10 μm in diameter are thought to be fairly easily absorbed, it is generally assumed that particles are 100% bioavailable after they are trapped in the lower lung. Likewise, it is generally assumed that most vapors and gases are completely absorbed (100% bioavailable) if they reach the lower respiratory tract. Both are conservative assumptions that should be reassessed on a case-by-case basis.

ROLE OF UNCERTAINTY ANALYSIS

Exposure assessment uses a wide array of information sources and techniques. Even when actual exposure-related measurements exist, assumptions or inferences will still be required. Most likely, data will not be available for all aspects of the exposure assessment and these data may be of questionable or unknown quality. In these situations, the exposure assessor will have to rely on a combination of professional judgment, inferences based on analogy with similar chemicals and conditions, estimation techniques, and the like. The net result is that the exposure assessment will be based on a number assumptions with varying degrees of uncertainty (U.S. EPA, 1992c).

The decision analysis literature has focused on the importance of explicitly incorporating and quantifying scientific uncertainty in risk assessments (Roseberry & Burmaster, 1991; Murray & Burmaster, 1994). Reasons for addressing uncertainties in exposure assessments include (U.S. EPA, 1992c):

- Uncertainty information from different sources and of different quality must be combined.
- A decision must be made about whether and how to expend resources to acquire additional information (e.g., production, use, and emissions data; environmental fate information; monitoring data; population data) to reduce the uncertainty.
- So much empirical evidence exists that biases may occur, resulting in so-called best estimates that are not very accurate. Even when all that is needed is a best-estimate answer, the quality of the answer may be improved by incorporating a frank discussion of uncertainty into the analysis.
- Exposure assessment is an iterative process. The search for an adequate and robust methodology to handle the problem at hand may proceed more effectively, and to a more certain conclusion, if the associated uncertainty is explicitly included and it can be used as a guide in the process of refinement.
- A decision is rarely made on the basis of a single piece of analysis. Further, it is rare for there to be one discrete decision; a process of multiple decisions spread over time is the more common occurrence. Chemicals of concern may go through several levels of risk assessment before a final decision is made. During this process, decisions may be made based on exposure considerations. An exposure analysis that attempts to characterize the associated uncertainty allows the user or decision maker to conduct a better evaluation in the context of the other factors being considered.
- Exposure assessors have a responsibility to present not just numbers, but also a clear and explicit explanation of the implications and limitations of their analyses. Uncertainty characterization helps to achieve this.

Essentially, constructing scientifically sound exposure assessments and analyzing uncertainty go hand-in-hand. The reward for analyzing uncertainties is knowing that the results have integrity or that significant gaps exist in available information that can make decision making a tenuous process.

Variability Versus Uncertainty

While some authors treat variability as a specific component of uncertainty, the U.S. EPA (Carrington & Bolger, 1998) and others advise risk assessors (and, by analogy, the exposure assessor) to distinguish between variability and uncertainty (National Research Council, 1994). Specifically, uncertainty represents a lack of knowledge about factors affecting exposure or risk, whereas variability arises from true heterogeneity across people, places, or time. In other words, uncertainty can lead to inaccurate or biased estimates, whereas variability can affect the precision of the estimates and the degree to which they can be generalized.

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Variability and uncertainty can complement or confound one another. The National Research Council (1994) has drawn an instructive analogy based on estimating the distance between the earth and the moon. Prior to fairly recent technological developments, it was difficult to accurately measure this distance, resulting in measurement uncertainty. Because the moon's orbit is elliptical, the distance is a variable quantity. If only a few measurements were taken without knowledge of the elliptical pattern, then either of the following incorrect conclusions might be reached:

- The measurements were faulty, thereby ascribing to uncertainty what was actually caused by variability; or
- The moon's orbit was random, thereby not allowing uncertainty to shed light on seemingly unexplainable differences that are in fact variable and predictable.

A more fundamental error in this situation might be to incorrectly estimate the true distance and assume that a few observations were sufficient. This latter pitfall—treating a highly variable quantity as if it were invariant or only uncertain—is most relevant to the exposure or risk assessor (U.S. EPA, 1992c).

Now consider a situation that relates to exposure, such as estimating the average daily dose by one exposure route—ingestion of contaminated drinking water. Suppose that it is possible to measure an individual's daily water consumption (and concentration of the contaminant) exactly, thereby eliminating uncertainty in the measured daily dose. The daily dose still has an inherent day-to-day variability, however, because of changes in the individual's daily water intake or concentration of the contaminant in the water (U.S. EPA, 1992c).

Clearly, it is impractical to measure the individual's dose every day. For this reason, the exposure assessor may estimate the average daily dose (ADD) based on a finite number of measurements, in an attempt to "average out" the day-to-day variability. The individual has a true (but unknown) ADD, which has now been estimated based on a sample of measurements. Because the individual's true average is unknown, it is uncertain how close the estimate is to the true value. Thus, the variability across daily doses has been translated into uncertainty in the ADD. Although the individual's true ADD has no variability, the estimate of the ADD has some uncertainty (U.S. EPA, 1992c).

The preceding discussion pertains to the ADD for one person. Now consider a distribution of ADDs across individuals in a defined population (e.g., the general U.S. population). In this case, variability refers to the range and distribution of ADDs across individuals in the population. By comparison, uncertainty refers to the exposure assessor's state of knowledge about that distribution, or about parameters describing the distribution (e.g., mean, standard deviation, general shape, various percentiles) (U.S. EPA, 1992c).

As noted by the National Research Council (1994), the realms of variability and uncertainty have fundamentally different ramifications for science and judgment. For example, uncertainty may force decision makers to judge how probable it is that exposures have been overestimated or underestimated for every member of the exposed population, whereas variability forces them to cope with the certainty that different individuals are subject to exposures both above and below any of the exposure levels chosen as a reference point (U.S. EPA, 1992c).

Types of Variability

Variability in exposure is related to an individual's location, activity, and behavior or preferences at a particular point in time, as well as pollutant emission rates and physical/chemical processes that affect concentrations in various media (e.g., air, soil, food, and water). The variations in pollutant-specific emissions or processes, and in individual locations, activities, or behaviors are not necessarily independent of one another. For example, both personal activities and pollutant concentrations at a specific location might vary in response to weather conditions, or between weekdays and weekends (U.S. EPA, 1992c).

At a more fundamental level, three types of variability can be distinguished:

- Variability across locations (spatial variability).
- Variability over time (temporal variability).
- Variability among individuals (inter-individual variability).

Spatial variability can occur both at regional (macroscale) and local (microscale) levels. For example, fish intake rates can vary depending on the region of the country. Higher consumption may occur among populations located near large bodies of water such as the Great Lakes or coastal areas. As another example, outdoor pollutant levels can be affected at the regional level by industrial activities and at the local level by activities of individuals. In general, higher exposures tend to be associated with closer proximity to the pollutant source, whether it be an industrial plant or related to a personal activity such as showering or gardening. In the context of exposure to airborne pollutants, the concept of a "microenvironment" has been introduced to denote a specific locality (e.g., a residential lot or a room in a specific building) where the airborne concentration can be treated as homogeneous (i.e., invariant) at a particular point in time.

Temporal variability refers to variations over time, whether long or short term. Seasonal fluctuations in weather, pesticide applications, use of woodburning appliances, and fraction of time spent outdoors are exam-

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ples of longer term variability. Examples of shorter term variability are differences in industrial or personal activities on weekdays versus weekends or at different times of the day.

Interindividual variability can be either of two types: (1) human characteristics such as age or body weight, and (2) human behaviors such as location and activity patterns. Each of these variabilities, in turn, may be related to several underlying phenomena that vary. For example, the natural variability in human weight is due to a combination of genetic, nutritional, and other lifestyle or environmental factors. Variability arising from independent factors that combine multiplicatively generally will lead to an approximately lognormal distribution across the population, or across spatial/temporal dimensions (U.S. EPA, 1992; Hoffman & Hammonds, 1992, 1994).

Monte Carlo Analysis

Among the most promising and exciting techniques to emerge in the area of exposure assessment in recent years is the application of Monte Carlo or other probabilistic analyses to environmental health issues (Morgan & Henrion, 1990; U.S. EPA, 1995; Duan & Mage, 1997). Monte Carlo analysis has existed as an engineering analytical tool for many years, but the development of the personal computer and software [e.g., Crystal Ball (Decisioneering, Boulder, CO), @RISK (Palisades Corp., Newfield, NY)] has allowed its application to new areas. As discussed previously, one criticism of many exposure assessments has been a reliance on overly conservative assumptions about exposure, as well as the problem of how to properly account for the highly exposed (but usually small) populations that do exist (Burmaster & Harris, 1993; Nichols & Zeckhauser, 1988). The Monte Carlo technique offers an approach to addressing this issue.

The probabilistic or Monte Carlo model accounts for the uncertainty in select parameters evaluating the range and probability of plausible exposure levels. Instead of specifying input parameters as single values, this model allows for consideration of the probability distributions. The Monte Carlo statistical simulation is a statistical model in which the input parameters to an equation are varied simultaneously. The values are chosen from the parameter distributions, with the frequency of a particular value being equal to the relative frequency of the parameter in the distribution. The simulation involves the following three steps:

1. The probability distribution of each equation parameter (input parameter) is characterized, and the distribution is specified for the Monte Carlo simulation. If the data cannot be fit to a distribution, the data are "bootstrapped" into the simulation, meaning that the input values are randomly selected from the actual data set without a specified distribution.

2. For each iteration of the simulation, one value is randomly selected from each parameter distribution, and the equation is run. Many iterations are performed, such that the random selections for each parameter approximate the distribution of the parameter. Five thousand iterations are typically performed for each dose equation.
3. Each iteration of the equation is evaluated and saved; hence a probability distribution of the equation output (possible doses) is generated.

This technique generates distributions that describe the uncertainty associated with the risk estimate (resultant doses). The predicted dose for every 5th percentile to the 95th percentile of the exposed population and the true mean are calculated. Using these models, the assessor is not forced to rely solely on a single exposure parameter or the repeated use of conservative assumptions to identify the plausible dose and risk estimates. Instead, the full range of possible values and their likelihood of occurrence is incorporated into the analysis to produce the range and probability of expected exposure levels (Finley et al., 1994b; Duan & Mage, 1997; Burmaster & von Stackelberg, 1991; Anderson & Yuhas, 1996; Burmaster & Anderson, 1994; R. L. Smith, 1994).

The methodology is illustrated in the following examples. The first example characterizes the time needed to go shopping. Time spent shopping each month (minutes) is estimated by the product of two parameters: the number of trips per month and the total time spent in the store (minutes). Total time spent in the store is the sum of time spent shopping and time spent waiting in line. Using Monte Carlo techniques, a distribution of likely values is associated with each of these parameters. These distributions depend upon the detail of information available to characterize each parameter. For example, the distribution compares all of the information, such as those days when the line at the check-out counter is short, as well as those when the line is long. It is noteworthy that each parameter has a different distribution: lognormal, gaussian, and square. Total time spent shopping is then calculated repeatedly by combining parameter values that are randomly selected from these distributions. The result is a distribution of likely time spent shopping each month. Using this technique, information concerning each parameter is carried along to the final estimate.

The second example, which directly applies to toxicologists, is to build a distribution that describes the various soil ingestion rates for children. As shown in Figure 6, the three pertinent distributions are the basis for constructing the overall exposure distribution.

Most of the variables used in an exposure assessment actually exist as ranges, rather than single point values and this is captaured in Monte Carlo analysis. For instance, the common assumption that adult body weight is 70 kg will be replaced by the appropriate distribution (i.e., normal) of body

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FIGURE 6. Example of how probability density functions (distributions) for three different related exposure factors are combined to form a distribution for the amount of soil ingested by a population of children. The Monte Carlo technique allows the risk assessor to account for the variability in many exposure parameters within a population and then produce a distribution that characterizes the entire population.

weights (including maximum, minimum, mean, and standard deviation). Using this approach, virtually every exposure variable, whether physiological, behavioral, environmental, or chronological, can be replaced with a probability distribution (Thompson & Burmaster, 1991; Finley et al., 1994a, 1994b; Price et al., 1996b; Burmaster & von Stackelberg, 1991; Anderson & Yuhas, 1996; Burmaster & Anderson, 1994; R. L. Smith, 1994; Glickman, 1986; Burmaster & Maxwell, 1991; Israeli & Nelson, 1992; Murray & Burmaster, 1992; Taylor et al., 1993; Ruffle et al., 1994; Thompson et al., 1992; Trowbridge & Burmaster, 1997; Burmaster & Thompson, 1995; Burmaster & Hull, 1997). Since no population (or individual) is exposed to a single concentration; breathes, eats, or drinks at a single rate; or is exposed for the same length of time, it is not appropriate to assess them as such. To be protective, high values are employed, resulting in the problems of compounding conservatisms mentioned previously (Maxim, 1989; Cullen, 1994; Burmaster & Harris, 1993; Allen et al., 1998; Frey & Rhodes, 1998).

The probabilistic analysis addresses the main deficiencies of the point estimate approach because it imparts more information to risk managers and the public, and uses all of the available data (Beck & Cohen, 1997; Mertz et al., 1998). The range of values (i.e., the distribution) for all the variables used in an exposure assessment is determined (e.g., normal, lognormal, uniform, triangular, etc.) and combined into a "distribution of distributions." Because of the extrapolations involved and the assumptions made, the area of single greatest uncertainty in risk assessment is associated with the dose-response evaluations.

It should also be clear that, in addition to exposure variables, data forming the basis of the toxicological criteria (carcinogenic potency factors [CPFs] and reference doses [RfDs]) are also amenable to Monte Carlo-style analysis where a robust database exists (Sielken, 1989; Shlyakhter et al., 1992; Evans et al., 1994a, 1994b; Velazquez et al., 1994; Baird et al., 1996; Cox, 1996; Crouch, 1996a, 1996b; Sielken & Valdez-Flores, 1996; Sielken & Stevenson, 1997; Hill & Hoover, 1997; Boyce, 1998). As with exposure variables, the advantage to this approach is that it allows all data to be used (and weighted appropriately, where necessary), thus avoiding reliance on a single experiment or endpoint.

Probabilistic analyses have in recent years been recognized in regulatory guidance (U.S. EPA, 1992b), and the U.S. EPA Risk Assessment Forum has published a document of principles for conducting Monte Carlo analyses (Cox, 1996) (Table 13). Recently, the U.S. EPA (1999b) published a comprehensive guidance document on how to conduct Monte Carlo assessments.

Like traditional exposure analysis, one challenge to performing a Monte Carlo analysis properly is having appropriate distributions for use in the analysis. Numerous studies on individual variables have been published in the risk assessment literature (Finley & Paustenbach, 1994; Beck & Cohen, 1997; Copeland et al., 1993, 1994; Gargas et al., 1999; Stanek &

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TABLE 13. U.S. EPA Guiding Principles for Monte Carlo Analysis

1. Conduct preliminary sensitivity analyses to identify important contributors to the assessment endpoint and its variability and uncertainty.
2. Based on the results of the sensitivity analyses, include probabilistic assessments only for the important pathways and parameters.
3. Use the entire database of information when selecting input distributions.
4. When using surrogate data, identify sources of uncertainty, and whenever possible, validate the use of these data by collecting site/case specific data.
5. If empirical data are collected for use in the assessment, use collection methods that improve the representativeness and quality of these data (especially at the tails of the distribution.)
6. Identify when expert judgment, rather than hard data, is used in the assessment.
7. Separate uncertainty and variability during the analysis.
8. Use appropriate methods to address uncertainty and variability, e.g., two-dimensional Monte Carlo.
9. Discuss the numerical stability of estimates at the tails of the distribution.
10. Identify which sources of uncertainty are addressed by the assessment, and which are not.
11. Provide a detailed description of all models used.
12. Provide a detailed description of the input distributions, including a distinction between variability and uncertainty in these distributions, and a graphical representation of the probability density and cumulative distribution functions.
13. Provide a graphical representation of the probability density and cumulative distribution functions of each output distribution.
14. Consider the potential covariance between important parameters. If the covariance cannot be determined, evaluate the impact of a range of potential covariances on the output distributions.
15. Present point estimates and identify where they fall on the exposure distribution. If there are large differences between point estimates and Monte Carlo estimates, explain if the differences are due to changes in the data or models used.
16. Present results in a tiered approach.

Note. From International Life Science Institute (1998).

Calabrese, 1995a, 1995b; U.S. EPA, 1997c; Burmaster, 1998a, 1998b; Sedman et al., 1998; Smith et al., 1992), and the impact on the distributions employed on the outcome has also been discussed (Hattis & Burmaster, 1994; Hoffman & Hammonds, 1994; Bukowski et al., 1995; Cooper et al., 1996; Haas, 1997; Hamed & Bedient, 1997). It should be pointed out that these techniques can be combined with other advanced risk assessment methods (i.e., PBPK modeling) to further reduce uncertainty in risk estimates (Cronin et al., 1995; Simon, 1997). Recently, two-dimensional Monte Carlo analyses have been developed that take into account both variability and uncertainty (Cullen & Frey, 1999; Vose, 1996). Information appropriate to probabilistic analyses can often be found in published papers in fields quite distant from the environmental sciences.

Case Study Using Monte Carlo Technique

An example might be useful (Gargas et al., 1999). Assume that persons are likely to be exposed to contaminated drinking water at the maximum contaminant limit (MCL). Concern has been raised that these regulatory limits are not sufficiently protective, and that certain federal and state regulatory programs (i.e., Resource Conservation and Recovery Act) are justified in requiring groundwater remediation to levels below that of

drinking water standards. To test this supposition, it is necessary to evaluate the possible incremental cancer risk of exposure via tap-water ingestion, dermal contact with water while showering, inhalation of indoor vapors, and ingestion of produce irrigated with groundwater, using a probabilistic approach. Probability density functions for each exposure variable (e.g., water ingestion, skin surface area, fraction of exposed skin, showering time, inhalation rate, air exchange and water use rates, exposure time, etc.) are then identified and used in the appropriate exposure equation to calculate dose and risk. A commercially available software package (i.e., @RISK) could be used to conduct the Monte Carlo analysis (Trowbridge & Burmaster, 1997).

Some have suggested that the Latin hypercube (LHC) approach offers some advantages to traditional approaches for identifying the correct number of iterations. Often, one can reach convergence sooner with LHC than the Monte Carlo option in @RISK/Crystal Ball. In addition, LHC is more reproducible (to the hundredth decimal place). The Monte Carlo option needs more iterations to reach convergence.

The results of such an analysis are presented in Table 14 (Gargas et al., 1999). The risk associated with exposure to water at the current maximum contaminant level (MCL) level for four different contaminants, as well as the 50th and 95th percentile of exposure as determined by the probabilistic analysis, are shown. At the 50th percentile level ("the best estimate"), the risk ranges from 6×10^{-7} (tetrachloroethylene) to 9×10^{-6} (chloroform), while at the 95th percentile ("the upper-bound risk"), these risks range from 4×10^{-6} (tetrachloroethylene) to 1.5×10^{-4} (chloroform). These values can be compared to the point estimate risks calculated for the MCLs, which range from 7×10^{-6} (tetrachloroethylene) to 5.4×10^{-5} (vinyl chloride). For the 50th percentile (average) person, all calculated risks are within the range of "acceptable" risks adopted by regulatory authorities for Superfund sites (1×10^{-4} to 1×10^{-7}). For the 95th percentile person (upper bound), the risks are still mostly below the 1×10^{-4} benchmark risk level generally used to separate acceptable from unacceptable risks. For tetrachloroethylene, these results are 30 (50th percentile) to 3 (risk at the MCL) times below the reasonable maximum exposure (RME) risk of 2×10^{-5} developed by combining the 95th percentile values for each expo-

TABLE 14. Risks Calculated for Exposure to Four Halogenated Solvents in Water Using Probabilistic Analysis at the MCL Level and for the 50th and 95th Percentile Exposure

Chemical	50th Percentile risk	95th Percentile risk	MCL risk
Tetrachloroethylene	0	0.000005	0.000007
Chloroform	0.000009	0.00014	0.000017
Bromoform	0.000002	0.000016	0.000023
Vinyl chloride	0.000005	0.000029	0.000054

Note. Adapted from Finley and Paustenbach (1994).

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sure variable using standard U.S. EPA risk assessment methodologies. This point estimate is greater than the 99th percentile of risk and is consistent with statements regarding the conservatism of the RME approach. These results suggest that chemical residues in drinking water at the MCL levels will be health protective and that remedial goals based on de minimis requirements (1×10^{-6}) might be unnecessarily low (Gargas et al., 1999).

In terms of estimates for the reasonably maximally exposed (RME) individual, which often serve as the basis for regulatory decisions, several observations on the utility of probabilistic assessment can be made. First, exposure assessments that incorporate two to three direct exposure pathways usually show that the 95th percentile probabilistic estimates are three to five times below the traditional RME estimates. Second, for multipathway assessments that contain several indirect exposure pathways, the 95th percentile probabilistic estimates can be as much as an order of magnitude below the RME estimates. Third, when the number of distributions used in the exposure assessment is 10 or more, the difference between the 50th and 95th percentile estimates may be between 5 and 10. Finally, in such assessments, the difference between the RME estimates and the 95th percentile probabilistic estimates can be as high as 100 (Finley & Paustenbach, 1994). In the probabilistic approach to estimating exposure and risk, the complete range of potential risks can be illustrated along with the likelihood estimates and estimates of uncertainty associated with such risks. While the availability and confidence of distributions for exposure variables differ, risk assessors ought to take advantage of this and similar approaches in their risk assessments to advance and improve the process. Additionally, since the highest degree of uncertainty in risk assessment tends to be the CPFs, attention ought to be directed to applying probabilistic analysis to the development of toxicity criteria in a similar manner (Finley et al., 2000; Evans et al., 1994a; Velazquez et al., 1994).

Sensitivity Analysis

In addition to establishing exposure and risk distributions, probabilistic analysis can also identify variables with the greatest impact on the estimates and illuminate uncertainties associated with exposure variables through sensitivity analysis (Bogen & Spear, 1987; Iman & Helton, 1991; Shlyakhter, 1994; Robinson & Hurst, 1997; Rai & Krewski, 1998). This provides some insight into the confidence that resides in exposure and risk estimates, and has two important results. First, it identifies the inputs that would benefit most from additional research to reduce uncertainty and improve risk estimates. Second, assuming that a thorough assessment has been conducted, it is possible to phrase the results in more accessible terms, such as "the risk assessment of PCBs in smallmouth bass is based on a large amount of high-quality reliable data, and we have high confidence in the risk estimates derived. The analysis has determined that 90 percent of the increased cancer risk could be eliminated through a ban on carp and catfish, but there is no appreciable reduction in risk from extending such a ban to bass and trout."

Such a description provides all stakeholders with considerably more information than a simple point estimate of risk based on a traditional exposure and risk assessment (Paustenbach, 1995).

If the most "sensitive" exposure variables are based on limited or uncertain data, confidence in these estimates will be poor. Robust data sets, on the other hand, lead to increased confidence in the resulting estimates. In the preceding example involving smallmouth bass, sensitivity is defined as the ratio of the relative change in risk produced by a unit relative to change in the exposure variables used. A Gaussian approximation (the product of the normalized sensitivity and the standard deviation of the distribution) of intake was used to allow both sensitivity and uncertainty to be gauged. In this case, the true mean of each distribution was chosen as the baseline point value, and the differential value for each variable was calculated by increasing this value by 10%. For each variable, the differential value was substituted, the risks recalculated, and the baseline value replaced (Gargas et al., 1999). Sensitivity was calculated using the following formula:

$$\text{Sensitivity} = \frac{|\ \text{Risk}_{\text{baseline}} - \text{Risk}_{10\%}\ |}{|\ X_{\text{baseline}} - X_{10\%}\ |} \cdot |\sigma|$$

where X_{baseline} and $X_{10\%}$ are baseline and differential values for the variable X, and σ is the standard deviation for the distribution of variable X. The sensitivity of each variable relative to one another is assessed by summing the unitless sensitivity values and determining the relative percent that each variable contributes to the total.

Table 15 indicates which are the most important variables in a probabilistic analysis of tetrachloroethylene in household tap water. In this case, the most sensitive exposure variables in household exposure to tap water are exposure time in shower and exposure duration. Relatively small changes in these variables will result in relatively large changes in the risk estimates. Since these estimates are based on actual time-use studies and census information, this suggests a high level of confidence can be placed

TABLE 15. Results of Sensitivity Analysis for Tetrachloroethylene Exposure in Household Water

Exposure variable	Sensitivity (unitless)	Percentage rank
Shower exposure time	0.000004	55.0%
Exposure duration	0.000001	20.0%
Plant–soil partition factor	0	8.4%
Water ingestion rate	0	4.6%
Surface area of exposed skin	0	4.4%
Body weight	0	3.8%
Dermal permeability constant	0	1.8%
Skin fraction contacting water	0	1.5%

Note. Adapted from Finley and Paustenbach (1994).

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on this estimate, particularly if site-specific data are being used. If the critical variables (in terms of sensitivity) were not based on robust data, this would suggest that the risk assessment could be improved by additional research on these exposure variables. It is interesting that the form of the distribution chosen for the variables is less important than the validity of the data (Finley et al., 1993). When the empirical distribution of the tapwater ingestion rate from Ershow and Cantor (1989) was substituted with a lognormal distribution developed by Roseberry and Burmaster (1992), the resultant change in the risk estimates was less than 1% (Trowbridge & Burmaster, 1997).

In this case, the value of the sensitivity analysis is that it allows input variables to be ranked in order of importance and confidence in the output to be established to a higher degree than previously possible. As pointed out by the U.S. EPA, where possible, exposure assessors should report variability in exposures as numerical distributions and should characterize uncertainty as probability distributions. They need to identify clearly where they are using point estimates for 'bounding' potential exposure variables or estimates; these point estimates should not be misconstrued to represent, for example, the upper 95th percentile when information on the actual distribution is lacking (Sielken & Valdez-Flores, 1996). As noted by the U.S. EPA, such explicit presentation of the data reduces the temptation to use the exposure assessment process for veiling policy judgments (Graham et al., 1992).

ISSUES IN EXPOSURE ASSESSMENT

The field of exposure assessment will continue to benefit from ongoing research efforts. The following are some fruitful areas of ongoing research.

Bioavailability

Applied research that will improve the practice of exposure assessment include bioavailability, speciation, chemical fate, and the role of biological monitoring. Bioavailability has become an increasingly important issue in the exposure assessment process (Hrudey et al., 1996; Schoof & Nielsen, 1997; Paustenbach et al., 1997a; Ruby et al., 1999). Alexander (1995) has shown that a variety of organic chemicals in soil lose the ability to interact with biological receptors over time, despite the fact that the chemical concentration in soil remains largely the same. The alteration in bioavailability extends across the various routes of exposure as well (Shu et al., 1988; Lucier et al., 1986; Umbreit et al., 1986a, 1986b; Skrowronski et al., 1988; Wester et al., 1993a, 1993b; Ruoff et al., 1994). Inorganic compounds, even those posing a potentially significant degrees of hazard (i.e., cyanide) react similarly (Davis et al., 1992, 1993, 1997; Shifrin et al., 1996). These losses in hazard potential are presumably due to irreversible chemical interactions with soil constituents. Table 16 indicates that the

TABLE 16. Effect of Matrix and Aging on the Bioavailability of Lead from Soil

Treatment			
Lead acetate (ppm diet)	Soil lead (ppm)	Tibial lead (standard deviation)	Relative lead absorption
—	—	0.3 (0.3)	—
—	11.3	0	—
50	—	247 (10)	100
50	11.3	130 (30)	53
—	706	40 (6)	16
—	995	108 (26)	44
—	1080	37 (7.3)	15
—	1260	53.6 (7)	22
—	10420	173 (22)	70

Note. Lead acetate in the diet results in an increase in tibial lead, while lead acetate mixed with soil is only 50% as well absorbed. Aged lead from garden soil must reach high levels before significant absorption occurs. Adapted from Chaney et al. (1984).

bioavailability of lead added to soil is immediately halved and that it is further reduced over time (Chaney et al., 1984). This would suggest that an assumption of 100% bioavailability of this compound (and many others) from soil is erroneous. It is also clear that the environmental media in which the compound occurs will influence its uptake into the body (Ruoff et al., 1994). The U.S. EPA recognized this fact when it developed two reference doses (RfDs) for manganese depending on whether it occurred in solid matrices (e.g., food, soil, etc.) or water (U.S. EPA, 1998). One simple method to improve bioavailability estimates is to conduct extractions under more biologically relevant conditions.

Bench-scale extraction experiments in simulated gastric fluids or sweat can be used to inexpensively and accurately measure how readily environmental residues can be released from the media in which they occur (Ruby et al., 1992; Horowitz & Finley, 1993; Ruby et al., 1999). As with inhalation or ingestion of vapors or solutions, both the release and absorption rates of agents from an environmental matrix (i.e., soil) across biological membranes need to be incorporated into the risk assessment when such data are available, and generated when absent. This need is particularly great when assessing dermal exposure. The problem for materials in aqueous solutions is less problematic than from solid matrices (Leung & Paustenbach, 1994). For liquids, permeability constants expressed in terms of agent weight per unit area per time (mg/cm^2-min) have been developed for a number of agents, and in vivo and in vitro techniques or mathematical models exist to develop similar flux rates if needed (Bartek et al., 1972; Wester & Noonan, 1980; Guy et al., 1982; Surber et al., 1990; Frantz, 1990; Shatkin & Brown, 1991; Barber et al., 1992; McKone, 1993; Bogen, 1994; Bogen et al., 1998; Wester et al., 1993a). From soil, however, the

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typical approach in many risk assessments has been to assume a constant percent absorbed from soil adhered to skin as a default. For volatiles, an absorption rate of 25% has sometimes been used. For semivolatiles and inorganics, absorption rates of 10% and 1% have been used, respectively.

Some experimental data for absorption are available for a few agents (e.g., PCBs, DDT, dioxin, benzo[a]pyrene, etc.), suggesting that the simple assumption of a constant percentage absorbed may overestimate or underestimate the dose depending on the agent, cocontaminants, soil type, exposure duration, and similar considerations (Shu et al., 1988; Skrowronski et al., 1988; Wester et al., 1993a, 1993b). The impact of using this default approach results in an instantaneous dermal dose being assumed, regardless of whether the soil remains in contact with the skin for 1 min or 1 day. This assumption, together with the questionable route-to-route adjustment of toxicity criteria from oral to dermal, results in a predicted dermal absorption of agents from soil, which arguably should present a minor risk in most cases, being a major driver in the risk assessment of soilbound contaminants.

Chemical Fate

Risk assessors ought to incorporate information on the fate of chemicals in the environment in their exposure estimates, whenever possible (Davis et al., 1993). Many organic compounds tend to degrade over time, and may disappear from exposed surfaces relatively quickly or otherwise change (American Chemical Society [ACS], 1983; Paustenbach, 1989b). As already suggested, inorganic compounds may also undergo changes in the environment over time that affect their fates (Shifrin et al., 1996; Chaney et al., 1984). Influencing factors include degradation by sunlight, soil and water microbes, evaporation, and chemical interactions. The resultant changes can dramatically alter the outcome of exposure assessments (Paustenbach et al., 1997a; Davis et al., 1997). For instance, much of the criticism of incinerators has focused on the inhalation risk of dioxin emitted from the stacks. As it turns out, the environmental half-life of dioxin (as a vapor) is only 90 min because of photolytic degradation. In contrast, the half-life for dioxin in soil or fly-ash is 50 to 500 yr. The focus of concern is often not the main risk issue when environmental fate is considered because levels and availability change over time (Paustenbach et al., 1999). Incorporation of half-life data into risk assessments can have substantial benefits for improving understanding of the potential exposures and risks associated with a specific situation (Borgert et al., 1995).

In a similar manner, the risk from persistent contaminants (i.e., DDT) in fish has usually been assessed using results from the analysis of raw fish fillets in combination with assumptions about the size and number of fish meals. The effects of cleaning and cooking on these residues are not typically considered, but have been shown to be reduced substantially in many cases (i.e., 50% or greater) when cooked or processed (Morgan et al., 1997; Wilson et al., 1998). Since many of these risk assessments form the basis of fish advisories or bans with potentially significant economic repercussions, there is obviously an important reason to make these exposure estimates as accurate as possible. Additionally, since there are known health benefits to fish consumption, making recommendations against eating fish based on theoretical risk deserves careful evaluation (Thomas et al., 1997).

Biomarkers and Molecular Epidemiology

The past decade has witnessed a dramatic increase in the level of research activity, derivation of theoretical constructs, and development of practical applications for the direct measurement of biological events or responses that result from human exposure to xenobiotics (DeCaprio, 1997; Hattis, 1986). These measurements, conveniently grouped under the descriptor "biological markers" or "biomarkers," reflect molecular and/or cellular alterations that occur along the temporal and mechanistic pathways connecting ambient exposure to a toxicant and eventual disease. As such, an almost limitless array of biomarkers is theoretically available for assessment, and only a minute fraction of these has been recognized and investigated to date (Hattis, 1986; McMillan et al., 1994; Holdway, 1996). Some events that can technically be classified as biomarkers of chemical exposure (e.g., hematological changes following high levels of exposure to lead or benzene, acetylcholinesterase inhibition by organophosphates) have been measured for decades. However, the recent surge of interest in this field has been driven by technical advances in analytical chemistry and molecular genetic techniques and by the recognition that "classical" toxicology and epidemiology may not be able to alone resolve critical questions regarding causation of environmentally induced disease (DeCaprio, 1997).

Biomarkers are an important component of the emerging discipline of molecular epidemiology, which seeks to expand the capabilities and overcome the limitations of classical epidemiology by incorporating biological measurements collected in exposed humans (DeCaprio, 1997; Wolfe, 1996). Early efforts at utilizing biomarkers to make quantitative estimates of exposure and to predict human cancer risk were made by Ehrenberg and Osterman-Golkar (1980). Using ethylene oxide as a model xenobiotic, these investigators explored the use of macromolecular reaction products (i.e., hemoglobin adducts) as internal dosimeters. By employing hemoglobin adduction data, they predicted the level of ambient ethylene oxide that would correspond to a tumorigenic dose of γ-radiation, which they termed the "rad-equivalent dose." Seminal work in the area of biomarkers as applied to the molecular epidemiology of cancer was performed by Perera and Weinstein (1982), who proposed the use of such techniques to identify environmental contributors to human cancer incidence. Important early applications of biomarkers to characterize environmental and

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occupational exposure have also been explored by several other groups in the United States and abroad.

As presented in the original NRC report, biomarkers of internal dose reflect the absorbed fraction of a xenobiotic, that is, the amount of material that has successfully crossed physiological barriers to enter the organism. Consequently, the magnitude of the biomarker accounts for bioavailability and is influenced by numerous parameters such as route of exposure, physiological characteristics of the receptor, and chemical characteristics of the xenobiotic. Generally, simple measurement of xenobiotic levels in biological media (blood, tissue, urine) can provide data on internal dose, and this is called biomonitoring (Ashley et al., 1994, 1996; Lynch, 1994). Biomarkers, on the other hand, reflect internal dose (in terms of proximity to downstream events in the sequence) and could include the measurement of a metabolite in selected biological media, particularly if such metabolite is active or critical to the toxic effects seen (DeCaprio, 1997).

Very useful exposure biomarkers for reactive xenobiotics or their activated (i.e., electrophilic) metabolites are macromolecular reaction products. Substantial research effort has been devoted to the use of protein and DNA adducts as molecular dosimeters. Ehrenberg and co-workers first proposed using hemoglobin (Hb) adducts to monitor the internal dose of alkenes and epoxides such as ethylene oxide over two decades ago (Ehrenberg & Osterman-Golkar, 1980). This methodology has since evolved into a widely-used and highly sensitive technique for quantitating N-terminal Hb adducts of a variety of xenobiotic metabolites in human blood. Hb adducts have been employed as internal exposure biomarkers for aromatic amines, nitrosamines, polycyclic aromatic hydrocarbons (PAHs), and other compounds (DeCaprio, 1997).

Protein and DNA adducts can be considered as biomarkers of either internal or biologically effective dose (BED), depending upon how close their relationship is to actual disease occurrence. The NRC report defined BED as dose at the site of action, dose at the receptor site, or dose to target macromolecules (National Research Council, 1987). This definition is troublesome since, strictly speaking, complete characterization of molecular site and mechanism of action for a given xenobiotic would be necessary in order to assign a particular measured end point as a marker of biologically effective dose. For example, protein adducts cannot be considered as effective dose biomarkers for carcinogens, since they do not satisfy these criteria. Ambiguity exists even for DNA adducts, since in no reported instance has xenobiotic-induced adduction of a specific base within a particular DNA sequence in a target cell type been unequivocally linked to a specific clinical outcome in people (DeCaprio, 1997). Despite these uncertainties, adducts in total lymphocyte DNA are considered as appropriate BED biomarkers for carcinogens, based upon the postulated mechanism of chemical carcinogenesis and limited experimental data indicating correlations between DNA adducts in lymphocytes and target tissues (DeCaprio, 1997).

Ideally, a biomarker should be biologically relevant, sensitive, and specific (i.e., valid). In addition, it should be readily accessible, inexpensive, and technically feasible. This combination of requirements is rarely achieved, and some trade-off is inevitable in order to obtain useful biomarker data in a timely manner. A few promising examples are presented in Table 17. The validation process for a biomarker involves determining the relationship between the biological parameter measured and both upstream and downstream events in the continuum, that is, the dose-response curve must be characterized (DeCaprio, 1997). For example, an Hb adduct considered for use as an exposure biomarker for a xenobiotic should exhibit a predictable relationship to ambient exposure level. In addition, if used as a surrogate for DNA adduction, then a reproducible correlation between Hb and DNA adducts must be demonstrated. Biological relevance refers to the nature of the phenomenon being measured and its mechanistic involvement in the pathway from exposure to disease. For biomarkers of exposure, disease relevance is not as critical a requirement as is a predictable exposure–response relationship; the opposite is true for biomarkers of effect (DeCaprio, 1997).

There are a few terms that are used when discussing biomarkers that help define their usefulness. *Sensitivity*, for example, reflects the ambient exposure level that can be detected by means of the biomarker. Highly sensitive markers are necessary to quantitate the low ambient levels typical of environmental exposures in industrialized Western nations. *Specificity* is the probability that the biomarker is indicative of actual exposure to the specific xenobiotic that it is designed to detect. For example, certain

TABLE 17. Biomarkers Examined for Selected Occupational and Environmental Chemicals

	Biomarker		
Chemical	Exposure	Effect	Susceptibility
PAH	DNA adducts[a] Hb adducts SA adducts Urinary 1-HP[a] Sister chromatid exchange (SCE) SCE (high-frequency cells)	*hprt* mutation *gpa* mutation *fes* oncogene activation *ras* p21 level DNA single-strand breaks Chromosomal aberrations Micronuclei	GST-M1 NAT-2 CYP1A1 CYP1A2
1,3-Butadiene	Hb adducts[a] Sister chromatid exchange (SCE) Urinary metabolites	*hprt* mutation Chromosomal aberrations Micronuclei *ras* oncogene activation	
Acrylamide	Hb adducts[a] Urinary metabolites		

Note. From DeCaprio (1997).
[a]Biomarkers for which cumulative data indicate best correlation with ambient exposure.

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macromolecular adducts can be derived from exposure to a number of chemical species and are thus less specific than one unique to a single compound. Biomarkers must also be reasonably accessible. Thus, with the exception of occasional tissue biopsies, samples for use in exposure biomarker studies generally consist of blood, urine, milk, or other readily obtainable biological media. Since these are rarely target tissues for toxicological or carcinogenic effects, how the concentration relates to the incidence of disease must be inferred. Finally, cost and technical feasibility are important considerations in selection of appropriate biomarkers for applied studies (DeCaprio, 1997).

Statistical and Analytical Issues

Despite the use of precise and reproducible analytical methods, we often do not have enough data of chemical concentrations to estimate exposure with great certainty. Due to resource availability, over the past 15–20 yr it has often been the case that a single round of analytical results or samples collected for other purposes (Graham et al., 1988) serves as input and the surrogate for long-term or lifetime exposure. As noted previously, chemical concentrations vary over both time and space, which makes the task of dose estimation all the more difficult (Morgan et al., 1997). For instance, to use the (estimated) average dose to predict the typical lifetime dose may seriously overestimate or underestimate the actual dose. Additionally, the average dose may be less important in the biological scheme of things than peak exposures or exposures at specific times (i.e., developmental effects), and ought to be considered as such in the evaluation of exposure (Andersen et al., 1987). Techniques do exist for estimating long-term exposure from short-term data (Slob, 1996; Buck et al., 1995, 1997), but the reliability of these estimates is uncertain. Similarly, various mathematical or bench-scale models exist that have been used to estimate exposure in the absence of measurements or long-term monitoring data (Stanek et al., 1998). As has been noted on several occasions, "all models are wrong, but some are useful," and risk assessors should carefully evaluate mesoscale and microscale models, as well as model outputs, for relevance and accuracy. Often, field measurements can serve as useful and relatively inexpensive "reality checks" on model results.

Equally important in exposure assessment are the statistics used to analyze field data. Environmental data are most often lognormally distributed. Under such conditions, a geometric average is generally assumed to be a better measure of the central tendency of data than the arithmetic mean (Crump, 1998). Despite this, the arithmetic mean (and the 95% upper confidence limit of the arithmetic mean) is typically used to identify environmental concentrations for use in exposure assessment. Since the advances in analytical chemistry have improved our ability to measure trace amounts of chemicals in different media and identify potential sources in some situations, less reliance should be placed on the use of mathematical models to predict the distribution of chemical and physical agents in the environment, and actual field data should be collected.

Another important issue in exposure assessment is how the analytical limit of detection (LOD) is handled in calculations. An agent reported as a nondetect may be treated as a numerical zero, or occurring at the LOD or some fraction of the LOD, typically one-half, for purposes of calculating statistics. The manner in which censured data are assessed may affect the outcome of the risk assessment process (Horwitz, 1984; Helsel, 1990; Perkins et al., 1990; Travis & Land, 1990; Gilbert, 1987; Haas & Scheff, 1990; Rappaport & Selvin, 1987; Parkin et al., 1988). For instance, analysis of highly contaminated samples or samples containing interfering substances may result in high LODs. Under such conditions and in the absence of additional analysis, assuming that nondetects are present at one-half the LOD could result in the exposure assessment and subsequent risk assessment being driven by compounds that are not truly present in the environmental media. When such an approach is used on a site that may be only 2 to 10% contaminated (based on surface area), the predicted severity of the level of contamination will be much higher than what actually occurs (Crump, 1998).

The practical result of these decisions can be illustrated by considering the following 11 data points resulting from analysis of field samples: Nondetect (ND), ND, ND, ND, ND, 5, 6, 6, 8, 55, and 500 ppm. The results are lognormally distributed as expected. The detection limit is 0.05 ppm, and nondetects are assumed to be present at one-half the detection limit (0.025 ppm). Using these assumptions, the arithmetic mean of the data set is 52.7 ppm, while the geometric mean is 1.3 ppm. The practical consequence of choosing one descriptor over the other may be to mischaracterize the dose and ultimately the risk, and this could influence regulatory decisions involving remediation or regulation.

CLOSING THOUGHTS

The field of exposure assessment has evolved significantly over the past 20 yr. We have learned a great deal about where people are exposed to xenobiotics and the relative degree of exposure. Not that long ago, most of our concerns were about industrial chemicals in our water, ambient air, and the soil. Today, we know that indoor exposure to particles, vapors, and gases (influenced by smoking) often represents the predominant source of exposure for most persons. A greater portion of our work in the future will undoubtedly focus on better understanding of both occupational and indoor exposure, rather than environmental exposures.

It is my personal view that of the four portions of a risk assessment, exposure assessment has made the biggest improvement in quality over the 20-yr history of health risk assessment. Often, exposure assessments will contain less uncertainty than other steps in a risk assessment, espe-

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cially the dose-response portion. Admittedly, there are a large number of factors to consider when estimating exposure, and it is a complicated procedure to understand the transport and distribution of a chemical that has been released into the environment. Nonetheless, the available data indicate that scientists can do an adequate job of quantifying the concentration of the chemicals in the various media and the resulting uptake by exposed persons if they account for all the factors that should be considered.

There are at least 11 significant lessons we have learned about conducting exposure assessments in recent years. Had we not had to learn through experience, avoiding these lessons could potentially have saved the United States hundreds of millions of dollars and thousands of person-years of work. First, experience has shown that in our attempts to be prudent, we placed too much emphasis on the "so-called" maximally exposed individual (MEI) (Nichols & Zeckhauser, 1988; Finley & Paustenbach, 1994). Often, the results of those analyses were misinterpreted by the public and/or misrepresented by some scientists or lawyers. Often, as a result, poor decisions were made by risk decision makers.

Second, as we have learned how to accurately characterize the risks of exposure for about 95% of the population, more emphasis has been placed on evaluating the various special groups (e.g., Eskimos, subsistence fishermen, dairy farmers). Although the risk for these populations, who can be exposed to particularly high doses (the 95–99.99% group), needs to be understood, the typical levels of exposure for the majority of the population should be the initial focus of the assessment. Perhaps the most significant change in exposure asesment of the past three years has been the national interest in characterizing the risks to children.

The third lesson is a variation of the second: Do not allow the repeated use of conservative assumptions to dictate the results of the assessment. In recent years, many investigators have addressed this issue and have demonstrated its importance. Monte Carlo techniques can generally be successful in addressing this problem.

Fourth, we have learned that risk managers and the public want to understand the statistical confidence in our estimates of risk. Sensitivity analyses can yield important information about the critical exposure variables (Rappaport & Selvin, 1987; Gilbert, 1987; Haas & Scheff, 1990; Travis & Land, 1990). Further, most risk assessments can benefit from analyses of both variability and uncertainty. Without these, risk managers are not fully informed.

Fifth, we have improved our techniques for statistically handling data; and particularly samples that have no detectable amount of a contaminant. In the past, regulatory agencies have used the limit of detection (LOD) of the analysis or one-half the LOD in the exposure calculations relying on the premise that the contaminant might be present at that level. We learned that when such an approach is used (without reflection) on a site that may only be 2–10% contaminated (based on surface area), the

impact of a few samples on the results could lead us to improper conclusions about the actual level of risk to persons who live there or nearby.

Sixth, we have gained a significant degree of confidence in our ability to estimate historical exposures; so called dose-reconstruction or retrospective risk assessments, a term that this author coined in 1983. Over the past ten years, for use in epidemiology studies, the likely exposure of workers and/or those in the community nearly forty to fifty years ago have been estimated using chemical usage and emission data, measured data and models (Ripple, 1992; Paustenbach et al., 1992c; Stewart & Herrick, 1991; Smith et al., 1993; Hallock et al., 1994; Widner, 2000).

Seventh, we now understand the need to quantitatively account for indirect pathways of exposure. For example, the uptake of a contaminant in water by humans due to ingestion is obvious (and direct), but the uptake of the same contaminant by garden vegetables due to watering and the uptake via the inhalation of volatile contaminants from the water while showering are indirect pathways that had not always been evaluated in assessments. Perhaps the most important indirect route of exposure, which had not been considered before 1986 when regulating airborne nonvolatile chemicals, was the ingestion of particulate emissions that has deposited onto soil and plants and were subsequently eaten by grazing animals (Fries & Paustenbach, 1990; U.S. EPA, 1997d). Much additional research in this area will be conducted, and the results will probably change our views about the hazards posed by numerous chemicals.

Eighth, we have learned that children and their exposure patterns are unlike those of adults. As some have said, in more ways than one, children are not miniature adults! Their intake of certain foods, percentage of time spent outdoors, proximity to carpets, and inhalation rates per body weight are all different than adults.

The ninth lesson learned is to use biological monitoring to validate or confirm the predicted degree of human exposure. Over the past 5 to 10 yr, analytical chemists have increased their ability to detect very small quantities of dozens of chemicals in blood, urine, hair, feces, breath, and fat. For many chemicals, these data represent a direct indicator of recent exposure, and in some cases (like PCBs and dioxins), chronic exposure. Validation of our exposure assessments should be one of the major areas of study during the next decade (through both biomonitoring and molecular epidemiology).

Tenth, it has become clear that in most cases, the most significant risks due to exposure to chemicals occurs in the workplace. Even though great strides have been made in industrial hygiene over the past 50 yr, the doses to which persons can legally be exposed are much greater (often by a factor of 100) than those to which most persons not in the community will ever be exposed.

Eleventh, and perhaps most important, we have learned that (for most persons) exposures to chemicals and bacteria in the home pose a greater risk than to those in the ambient air or through the ingestion of water. Many

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fine studies conducted in the 1970s through the current day continue to show that in-home exposures to most chemicals are often about 2–20 times greater than that present in the ambient environment (Gessell & Prichard, 1980; Jenkins et al., 1992; Daisey et al., 1994; Krieger et al., 1992; Lioy et al., 1988, 1990; Wallace, 2000b; Ott & Roberts, 1998). Recently, more than 200 scientists in the fields of epidemiology, exposure assessment, and medicine signed a document called a "consensus statement," which states that future research should focus on personal monitoring; especially of the indoor environment (Editor, 2000).

We have come a long way in a short time. Several professional societies, including the International Society of Exposure Analysis (ISEA), Society for Risk Analysis (SRA), American Industrial Hygiene Association (AIHA), Air and Waste Management Association (AWMA), American Chemical Society (ACS), Society of Toxicology (SOT), International Society for Regulatory Toxicology and Pharmacology (ISRTP), and others, have placed an emphasis on improving the practice of exposure assessment. All indications are that the information we have gained has significantly improved the quality of recent risk assessments, and it can be expected that due to better exposure assessments, future decisions by risk managers will be much better informed.

GLOSSARY OF TERMS

Most of these definitions were presented in the U.S. EPA *Exposure Assessment Guidelines.*

50th Percentile—The number in a distribution such that half the values in the distribution are greater than the number and half the values are less. The 50th percentile is equivalent to the median.

95th Percentile—The number in a distribution such that 95% of the values in the distribution are less than or equal to the number and 5% are greater.

95% Upper confidence limit for mean—The 95% upper confidence limit (95% UCL) for a mean is defined as a value that, when repeatedly calculated for randomly drawn subsets of size *n*, equals or exceeds the true population mean 95% of the time. Although the 95% UCL provides a conservative estimate of the mean, it should not be confused with a 95th percentile. As sample size increases, the difference between the UCL for the mean and the true mean decreases, while the 95th percentile of the distribution remains relatively unchanged, at the upper end of the distribution. The U.S. EPA Superfund program has traditionally used the 95% UCL for the mean as the concentration term in point estimates of RME for human health risk assessment.

Absorption barrier—Any of the exchange barriers of the body that allow differential diffusion of various substances across a boundary. Examples of absorption barriers are the skin, lung tissue, and gastrointestinal tract-wall.

Administered dose—The amount of a substance given to a test subject (human or animal) in determining dose-response relationships, especially through ingestion or inhalation. In exposure assessment, since exposure to chemicals is usually inadvertent, this quantity is called potential dose.

Aggregate risk—The likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a single substance.

Ambient measurement—A measurement (usually of the concentration of a chemical or pollutant) taken in an ambient medium, normally with the intent of relating the measured value to the exposure of an organism that contacts that medium.

Applied dose—The amount of a substance in contact with the primary absorption boundaries of an organism (e.g., skin, lung, gastrointestinal tract) and available for absorption.

Arithmetic mean—The sum of all the measurements in a data set divided by the number of measurements in the data set.

Background exposure—Exposures that are not related to the site. For example, exposure to chemicals at a different time or from locations other than the exposure unit of concern. Background sources may be either naturally occurring or anthropogenic (man-made).

Background level (environmental)—The concentration of substance in a defined control area during a fixed period of time before, during, or after a data-gathering operation.

Bioavailability—The state of being capable of being absorbed and available to interact with the metabolic processes of an organism. Bioavailability is typically a function of chemical properties, physical state of the material to which an organism is exposed, and the ability of the individual organism to physiologically take up the chemical.

Biologically effective dose—The amount of a deposited or absorbed chemical that reaches the cells or target site where an adverse effect occurs, or where that chemical interacts with a membrane surface.

Body burden—The amount of a particular chemical stored in the body at a particular time. Body burdens can be the result of long-term or short-term storage [for example, the amount of a metal in bone, the amount of a lipophilic substance such as PCB in adipose tissue, or the amount of carbon monoxide (as carboxyhemoglobin) in the blood].

Bootstrap—A method of sampling actual data at random, with replacement, to derive an estimate of a population parameter such as the arithmetic mean or the standard error of the mean. The sample size of each bootstrap sample is equal to the sample size of the original data set. Both parametric and nonparametric bootstrap methods have been developed.

Bounding estimate—An estimate of exposure, dose, or risk that is higher than that incurred by the person in the population with the highest exposure, dose, or risk. Bounding estimates are useful in developing

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statements that exposures, doses, or risks are "not greater than" the estimated value.

Central tendency exposure (CTE)—A risk descriptor representing the average or typical individual in the population, usually considered to be the arithmetic mean or median of the risk distribution.

Cumulative distribution function (CDF)—A representation, generally a function or graph, of the cumulative probability of occurrence for a random independent variable. The CDF is obtained from the PDF by integration in the case of a continuous random variable and by summation for discrete random variables. Each value c of the function is the probability that a random observation x will be less than or equal to c.

Cumulative risk—The likelihood of an occurrence of an adverse health effect resulting from all routes of exposure to a group of substances sharing a common mechanism of toxicity.

Dose—The amount of a substance available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. The *potential dose* is the amount ingested, inhaled, or applied to the skin. The *applied dose* is the amount of a substance presented to an absorption barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism). The *absorbed dose* is the amount crossing a specific absorption barrier (e.g., the exchange boundaries of skin, lung, and digestive tract) through uptake processes. *Internal dose* is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries. The amount of the chemical available for interaction by any particular organ or cell is termed the *delivered dose* for that organ or cell.

Dose rate—Dose per unit time, for example in mg/d, sometimes also called dosage. Dose rates are often expressed on a per unit body weight basis, yielding units such as mg/kg/d (mg/kg-d). They are also often expressed as averages over some time period, such as a lifetime.

Dose reconstruction—An approach to quantifying exposure which has occurred in the past. One approach relies upon internal dose, which is in turn reconstructed after exposure has occurred, from evidence within an organism such as chemical levels in tissues or fluids, or from evidence of other biomarkers of exposure. An alternative approach is to estimate the likely absorbed dose using historical exposure data, models, assumptions, and field data.

Dosimetry—Process of measuring or estimating dose.

Empirical distribution—A distribution obtained from actual data and possibly smoothed with interpolation techniques. Data are not fitted to a particular parametric distribution (e.g., normal, lognormal), but are described by the percentile values.

Environmental fate—The destiny of a chemical or biological pollutant after release into the environment. Environmental fate involves temporal and spatial considerations of transport, transfer, storage, and transformation.

Exposure—Contact of a chemical, physical, or biological agent with the outer boundary of an organism. Exposure is quantified as the concentration of the agent in the medium in contact integrated over the time duration of that contact.

Exposure assessment—The qualitative or quantitative estimate (or measurement) of the magnitude, frequency, duration, and route of exposure. A process that integrates information on chemical fate and transport, environmental measurements, human behavior, and human physiology to estimate the average doses of chemicals received by individual receptors. For simplicity in this guidance, exposure encompasses concepts of absorbed dose (i.e., uptake and bioavailability).

Exposure concentration—The concentration of a chemical in its transport or carrier medium at the point of contact.

Exposure pathway—The physical course a chemical or pollutant takes from the source to the organism exposed.

Exposure point concentration (EPC)—The contaminant concentration within an exposure unit to which receptors (people) are exposed. Estimates of the EPC represent the concentration term used in exposure assessment.

Exposure route—The way a chemical or pollutant enters an organism (e.g., by ingestion, inhalation, or dermal absorption).

Exposure scenario—A set of facts, assumptions, and inferences about how exposure takes place that aids the exposure assessor in evaluating, estimating, or quantifying exposures.

Frequency distribution—A graph or plot that shows the number of observations that occur within a given interval; usually presented as a histogram showing the relative probabilities for each value. It conveys the range of values and the count (or proportion of the sample) that was observed across that range.

Geometric mean—The nth root of the product of n values.

High-end exposure (dose) estimate—A plausible estimate of individual exposure or dose for those persons at the upper end of an exposure or dose distribution, conceptually above the 90th percentile, but not higher than the individual in the population who has the highest exposure or dose.

High-end risk descriptor—A plausible estimate of individual risk for those persons at the upper end of the risk distribution, conceptually above the 90th percentile but no higher than the individual in the population with the highest risk. Note that persons in the high end of the risk distribution have high risk due to high exposure, high susceptibility, or other reasons; therefore, persons in the high end of the exposure or dose distribution are not necessarily the same individuals as those in the high end of the risk distribution.

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Intake—The process by which a substance crosses the outer boundary of an organism without passing an absorption barrier (e.g., through ingestion or inhalation). See also *potential dose*.

Internal dose—The amount of a substance penetrating across the absorption barriers (the exchange boundaries of an organism) via physical or biological processes.

Kriging—A statistical interpolation method that selects the best linear unbiased estimate of the parameter in question. Often used as a geostatistical method of spatial statistics for predicting values at unobserved locations based on data from the surrounding area. Information on fate and transport of chemicals within the area lacking data can be incorporated into kriged estimates.

Latin hypercube sampling (LHS)—A variant of the Monte Carlo sampling method that ensures selection of equal numbers of values from all segments of the distribution. LHS divides the distribution into regions of equal sampling coverage. Hence, the values obtained will be forced to cover the entire distribution. It is more efficient than simple random sampling, that is, it requires fewer iterations to generate the distribution sufficiently.

Limit of quantification (LOQ)—The concentration of analyte in a specific matrix for which the probability of producing analytical values above the method detection limit is 99%.

Maximally exposed individual (MEI)—The single individual with the highest exposure in a given population (also, most exposed individual). This term has historically been defined in various ways, including as defined here and also synonymously with worst case or bounding estimate. Assessors are cautioned to look for contextual definitions when encountering this term in the literature.

Median value—The value in a measurement data set such that half the measured values are greater and half are less.

Microenvironments—Well-defined surroundings such as the home, office, automobile, kitchen, store, etc. that can be treated as homogeneous (or well characterized) in the concentrations of a chemical or other agent.

Microexposure event (MEE) analysis—A method of assessing risk based on an aggregate sum of a receptor's contact with a contaminated medium. MEE analysis simulates lifetime exposure as the sum of many short-term, or "micro," exposures. MEE approaches can be used to explore uncertainty associated with the model time step in probabilistic risk assessment (e.g., use of a single value to represent a long-term average phenomenon, seasonal patterns in exposure, or intraindividual variability).

Monte Carlo technique—A repeated random sampling from the distribution of values for each of the parameters in a generic (exposure or dose) equation to derive an estimate of the distribution of (exposures or doses in) the population.

Nonparametric statistical methods—Methods that do not assume functional form with identifiable parameters for the statistical distribution of interest (distribution-free methods).

Personal measurement—A measurement collected from an individual's immediate environmental using active or passive devices to collect the samples.

Pharmacokinetics—The study of the time course of absorption, distribution, metabolism, and excretion of a foreign substance (e.g., a drug or pollutant) in an organism's body.

Point estimate—A quantity calculated from values in a sample to represent an unknown population parameter. Point estimates typically represent a descriptive statistic (e.g., arithmetic mean, 95th percentile).

Point estimate risk assessment—The traditional risk assessment methodology in which a single estimate of risk is calculated from a set of point estimates. The results provide point estimates of risk for the central tendency exposure (CTE) and reasonable maximum exposure (RME) exposed individuals. Variability and uncertainty are discussed in a qualitative manner.

Point-of-control measurement of exposure—An approach to quantifying exposure by taking measurements of concentration over time at or near the point of contact between the chemical and an organism while the exposure is taking place.

Potential dose—The amount of a chemical contained in material ingested, air breathed, or bulk material applied to the skin.

Precision—A measure of the reproducibility of a measured value under a given set of conditions.

Probabilistic risk assessment (PRA)—A risk assessment that uses probabilistic methods to derive a distribution of risk or hazard based on multiple sets of values sampled for random variables.

Probability density function (PDF)—A representation, generally a function, graph, or histogram, of the probability of occurrence of an unknown or variable quantity. The sum of the probabilities for discrete random variables, and the integral for continuous random variables (i.e., the area under the curve) is equal to 1.0. PDFs can be used to display distributions used as input to a probabilistic assessment or the distribution of risks that forms the output of the assessment.

Reasonable maximum exposure (RME)—The highest exposure that is reasonably expected to occur at a site. The intent of the RME is to estimate a conservative exposure case (i.e., well above the average case) that is still within the range of possible exposures.

Reasonable worst case—A semiquantitative term referring to the lower portion of the high end of the exposure, dose, or risk distribution. The reasonable worst case has historically been loosely defined, including synonymously with maximum exposure or worst case, and assessors

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are cautioned to look for contextual definitions when encountering this term in the literature. As a semiquantitative term, it is sometimes useful to refer to individual exposures, doses, or risks that, while in the high end of the distribution, are not in the extreme tail. For consistency, it should refer to a range that can conceptually be described as above the 90th percentile in the distribution, but below about the 98th percentile (compare maximum exposure range, worst case).

Remediation action level (RAL)—A concentration such that remediation of all concentrations above this level in an exposure unit will result in the 95% UCL being reduced to a level that does not pose an unacceptable risk to an individual experiencing random exposures. The RAL will depend on the mean, variance, and sample size of the concentrations within an exposure unit as well as considerations of short-term effects of the chemicals of concern.

Risk characterization—A component of risk assessment that describes the nature and magnitude of risk, including uncertainty. In assessments of Superfund sites, it includes the summary and interpretation of information gathered from previous steps in the site risk assessment (e.g., data evaluation, exposure assessment, toxicity assessment), including the results of a probabilistic analysis.

Statistical significance—An inference that the probability is low that the observed difference in quantities being measured could be due to variability in the data rather than an actual difference in the quantities themselves. The inference that an observed difference is statistically significant is typically based on a test to reject one hypothesis and accept another.

Uncertainty—Lack of knowledge about specific variables, parameters, models, or other factors. Examples include limited data regarding the concentration of a contaminant in an environmental medium and lack of information on local fish consumption practices. Uncertainty may be reduced through further study.

Variability—True heterogeneity, diversity, or a range that characterizes an exposure variable or response (e.g., differences in body weight). Further study (e.g., increasing sample size, *n*) will not reduce variability, but it can provide greater confidence in quantitative characterizations of variability.

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